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METHODS FOR PREVENTING OR ATTENUATING PATHOANGIOGENIC CONDITIONS

Abstract:

Abstract of WO0156598

Methods are provided for preventing or attenuating pathoangiogenic conditions by administering at least one GBS toxin receptor polypeptide or at least one immunogenic fragment thereof. Also provided are a composition that includes a GBS toxin receptor polypeptide and a method for making such a composition. In another embodiment of the invention, immunized animals also receive GBS toxin, immunocompatible antibodies to the GBS toxin receptor, and/or expanded autologous T cells to the GBS toxin receptor. Also included in this invention are methods of identifying additional GBS toxin receptors.

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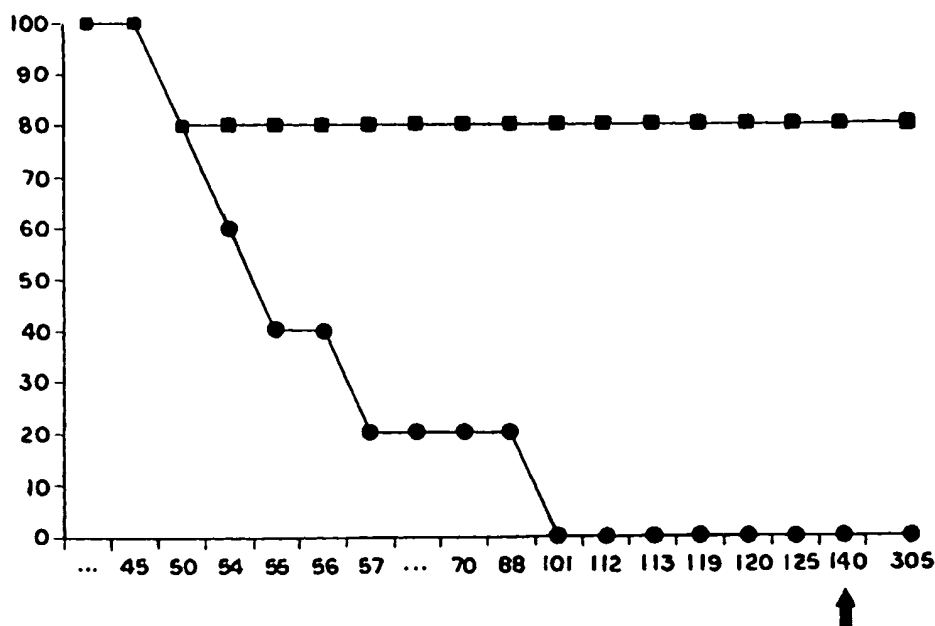
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(54) Title: METHODS FOR PREVENTING OR ATTENUATING PATHOANGIOGENIC CONDITIONS



(57) Abstract: Methods are provided for preventing or attenuating pathoangiogenic conditions by administering at least one GBS toxin receptor polypeptide or at least one immunogenic fragment thereof. Also provided are a composition that includes a GBS toxin receptor polypeptide and a method for making such a composition. In another embodiment of the invention, immunized animals also receive GBS toxin, immunocompatible antibodies to the GBS toxin receptor, and/or expanded autologous T cells to the GBS toxin receptor. Also included in this invention are methods of identifying additional GBS toxin receptors.

WO 01/56598 A2

## **METHODS FOR PREVENTING OR ATTENUATING PATHOANGIOGENIC CONDITIONS**

### **TECHNICAL FIELD**

This invention provides methods and compositions for preventing or ameliorating medical conditions arising from the formation of pathological neovasculture. These conditions include cancer, scarring during wound healing, keloid formation, chronic wounds, gliosis during repair of nerve injury, reperfusion injury, rheumatoid arthritis, psoriasis and atherosclerosis.

### **BACKGROUND**

Cancer is the second leading cause of death in the United States, second only to heart disease (which is frequently due in part to atherosclerosis). Since 1990 approximately 12 million new cases of cancer have been diagnosed and five million persons have died of cancer in the United States.

Neural injury can result in death or profound disability such as loss of movement, impaired sensory perception, loss of cognitive functions, seizures, and emotional and personality disorders.

Rheumatoid arthritis (RA) and psoriasis are prevalent chronic inflammatory diseases propagated by inflammatory angiogenesis. RA affects approximately 1-2% of the world's population. RA sufferers often experience pain and impaired mobility, and as a group they have twice the mortality rate of their unaffected counterparts. Approximately 1-3% of United States residents and an even higher percentage of Northern Europeans suffer from psoriasis, a disease in which the skin develops recurrent erythematous plaques that burn and itch.

Chronic wounds or skin ulcers are major problems in diabetic and geriatric populations. Poor healing of acute wounds inflicted by accidents or surgical incisions and the formation of wound-associated scars seriously impair recovery from such events. Reperfusion injuries cause damage to transplanted organs as well as tissues near the site of surgical intervention, stroke or heart attack.

There is a need for a prophylaxis that would prevent cancer, gliosis during repair of nerve injury, chronic inflammatory diseases such as rheumatoid arthritis and psoriasis, scarring during wound healing, keloid formation, chronic wounds, reperfusion injury and atherosclerosis. There is also a need for an effective and safe therapy for each of these medical conditions.

## SUMMARY OF THE INVENTION

The present invention provides a method for preventing or protecting against pathoangiogenic conditions by administering one or more Group B  $\beta$ -hemolytic *Streptococci* (GBS) toxin receptors or immunogenic fragments thereof to a mammal in an amount sufficient to induce or maintain an immune response to at least one of the GBS toxin receptors.

The present invention also provides a method for decreasing the incidence of, ameliorating, lessening the severity of, or attenuating pathoangiogenic conditions by administering one or more GBS toxin receptors or immunogenic fragments thereof to a mammal in an amount sufficient to induce or maintain an immune response to at least one of the GBS toxin receptors.

Another aspect of the present invention is a vaccine comprising one or more GBS toxin receptors or immunogenic fragments thereof in combination with a pharmaceutically acceptable excipient.

The pathoangiogenic conditions that can be prevented or attenuated by the methods and compositions of the present invention include cancer, scarring during wound healing, keloid formation, chronic wounds, gliosis during repair of nerve injury, reperfusion injury, rheumatoid arthritis, psoriasis and atherosclerosis.

Preferred GBS toxin receptors are HP59 and SP55 and substantially identical variants thereof. Mammals treated with the methods or the compositions of the present invention may be additionally treated with GBS toxin, with immunocompatible antibodies directed at the GBS toxin receptor, or with autologous activated GBS toxin receptor-recognizing T cells.

Yet another aspect of the present invention is a method for making a composition for the treatment and/or prevention of pathoangiogenic conditions. This method involves providing one or more GBS toxin receptors or immunogenic fragments thereof, and formulating it in a pharmaceutically acceptable excipient. An adjuvant may optionally be provided.

## BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 presents growth curves for Lewis Lung tumors in control mammals and in male and female mammals immunized with a composition of the present invention. The y-axis represents tumor volume and the x-axis represents the day the tumor volume was measured. Male controls are denoted by blackened diamonds, female controls are denoted by blackened circles; male immunized are denoted by clear circles and female immunized are denoted by clear diamonds.

Fig. 2 presents survival curves for female mammals immunized with a composition of the present invention and challenged intravenously with melanoma cells and for female control mammals equally challenged but not immunized. The y-axis represents percentage of survivors and the x-axis represents the number of days of survival. The blackened circles denote female controls and the blackened squares denote female immunized mammals.

## DESCRIPTION OF SPECIFIC EMBODIMENTS

## INTRODUCTION

Group B  $\beta$ -hemolytic *Streptococci* (GBS) are ubiquitous microorganisms that are generally harmless to humans with one exception – newborn infants infected with GBS frequently develop GBS pneumonia (also called “early onset disease” or “early onset septicemia”), a disease that is associated with high morbidity and mortality. Hellerqvist and colleagues identified a polysaccharide GBS toxin that is a major factor in the complications of GBS pneumonia (Hellerqvist, C.G. *et al.*, *Pediatr. Res.*, 12:892-898 (1981); Sundell, H. *et al.*, *J. Pediatr.* 137: 338-344 (2000)).

GBS toxin was subsequently found to have many therapeutic properties. It is an anticancer agent that inhibits vascularization of solid tumors (U.S. Patent No. 5,010,062 and corresponding European Patent No. EP 0 445 280 B1; DeVore *et al.* (1997) *Clinical Cancer Res.* 3,365-372)). In addition, as described in U.S. Patent No. 5,858,991 and WO98/32453, GBS toxin facilitates wound healing in mammals by minimizing scarring and accelerating healing, and reduces wound-related tumor progression. GBS toxin also enhances repair of neural injuries by minimizing the formation of glial scars (U.S. Patent No. 5,981,508 and WO98/32448) and ameliorates the symptoms of certain chronic inflammatory diseases such as rheumatoid arthritis and psoriasis (WO98/32452).

GBS toxin's anticancer effect has been traced to its ability to rapidly bind tumor-associated endothelial cells and to subsequently activate complement by the alternate (C3) pathway. Activated leukocytes soon infiltrate the endothelial cells, which are subsequently destroyed, and the tumors shrink as a result of the inflammatory response and insufficient blood supply (Yan *et al.*, *Angiogenesis* 2:219-233 (1998); Wamil, B.D. *et al.*, *AACR Proceedings*, 38:237 (1997)).

Without limitation to a particular theory, it is believed that GBS toxin's other therapeutic effects are due to a similar mechanism. Nerve trauma, wounds, disruption of blood flow, reperfusion, atherosclerotic plaques, rheumatoid arthritis and psoriasis all induce hypoxia which in turn causes the release of vascular endothelial growth factor (VEGF) (Liu *et al.*, *J. Neuroscience* 17:5395-5406 (1997)). VEGF stimulates endothelial cells to dedifferentiate and begin forming new vasculature by a process known as pathological angiogenesis and also known as pathoangiogenesis. In patients with neural injuries, the newly formed vasculature facilitates gliosis, a proliferation of glial cells which gives rise to glial scars that sterically interfere with re-establishment of neuronal connectivity. Neovasculature in the joints of rheumatoid arthritis sufferers facilitates synovial tissue hyperplasia, pannus formation, and cartilage destruction. Similarly, pathological angiogenesis facilitates the establishment, maintenance and enlargement of psoriatic lesions and is a driving force in the formation of granulation tissue, which leads to chronic wounds or scar formation (including keloids) in the vicinity of wounds. In atherosclerosis, the pathological neovasculature provides oxygen and nutrients to smooth muscle and endothelial cells located below plaques and results in further narrowing of affected blood vessels. Other conditions caused by pathological angiogenesis include diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, angiofibromas, immune and non-immune inflammation, hemangiomas, Kaposi's sarcoma, and endometriosis (see PCT Publication Number WO 91/10424, page 13, lines 14-21). Additional conditions caused by pathological angiogenesis include corneal graft neovascularization, ocular tumors, trachoma, and hemophiliac joints (see European Patent Application Publication Number EP 0 325 199 A2, page 2, lines 12-19). Additional conditions caused by pathological angiogenesis include retinopathy of prematurity, macular degeneration, Behcet's syndrome, Osler-Weber-Rendu disease, osteoarthritis, corneal graft rejection and ocular neovascular diseases (see PCT Publication Number WO 94/20085, page 2, line 27 to page 6, line 14). GBS toxin interferes with these harmful processes by binding to the budding pathological neovasculature and targeting it for destruction by the immune system.

It was believed that GBS toxin attacks the lungs of human neonates and binds embryonic neovasculature via receptors present on these tissues at birth and for a short time (about 7 days in term babies and longer in premature infants) thereafter. It was further hypothesized that the same receptors are present later in life only upon pathological neovasculature (i.e. new capillaries formed by pathological angiogenesis). This belief has been confirmed by the recent identification of novel proteins found on such cells that specifically bind GBS toxin. The nucleic acid and amino acid sequences of the human GBS toxin receptor known as HP59 are shown in SEQ ID NO:1 and SEQ ID NO:2, respectively (GenBank Accession Number AF244578). The nucleic acid and amino acid sequences of the sheep GBS toxin receptor known as SP55 (cloned from a sheep lung library, GenBank Accession Number AF244578) are shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. Both HP59 and SP55 are integral proteins with multiple transmembrane domains. Each has several putative sites for phosphorylation by cAMP-dependent kinase, protein kinase C (PKC) and casein kinase II (CK2) as well as putative sites for glycosylation and myristylation. Although HP59 has 41 amino acids at its amino terminus that SP55 lacks, the two proteins are otherwise 87% identical.

As expected, GBS toxin receptor is expressed on the lungs of human neonates and sheep (which are susceptible to infection by GBS). It is not expressed in the vasculature associated with normal (healthy, non-neonate) human ovary, colon, breast or lung tissue, but it is present in the vasculature of tumors in these tissues. Thus, GBS toxin receptor expression is correlated with medical conditions involving pathologic angiogenesis and the receptor is not seen in healthy tissue from humans who are more than one month old (except for premature babies, in which expression is correlated with their due dates).

Although not wishing to be bound by theory, it is believed that since the GBS toxin receptor is present on the pathological neovasculature associated with pathoangiogenic conditions, the immune system, if primed to recognize the GBS toxin receptor, will attack such forming vasculature and the pathoangiogenic condition will be prevented or attenuated. Therefore, the present invention involves methods and compositions for invoking an immune response to the GBS toxin receptor.

## DEFINITIONS

Generally, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The nomenclature used herein and the laboratory procedures in immunology, cell culture,

biochemistry and molecular biology described below are those well known and commonly employed in the art. Standard techniques are used for recombinant nucleic acid methods, polypeptide synthesis, and production of monoclonal and polyclonal antibodies. Enzymatic reactions and purification steps supplied by manufacturers are typically performed according to the manufacturer's specifications. The techniques and procedures are generally performed according to conventional methods in the art and various general references (*See generally, Sambrook et al., Molecular Cloning: A Laboratory Manual*, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.) which are provided throughout this document. The nomenclature used herein and the laboratory procedures in analytical chemistry, organic synthetic chemistry, immunology and pharmaceutical formulation described below are those well known and commonly employed in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical formulation and delivery, and treatment of mammals. As employed throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

For the purposes of this invention, the term "GBS toxin" means any purified fraction or component of the natural GBS toxin, or derived from media or protease digests of lysed GBS bacterial; and whose toxicity can be confirmed by either of the following specified assay procedures. The potency of isolated GBS toxin as a tumor growth inhibitor may be ascertained by peroxidase-antiperoxidase (PAP) assays of tumor tissue specimens using anti-GBS toxin IgG, and by infusion in a sheep model at 2  $\mu$ gs  $10^{-11}$  moles per kg (Hellerqvist, C.G. *et al.*, 1981, cited above; Hellerqvist, C.G. *et al. PNAS* 84:51-56 (1987)).

"GBS toxin receptor" means a proteinaceous molecule capable of binding a toxin from Group B  $\beta$ -hemolytic *Streptococcus* bacteria (GBS toxin). A GBS toxin receptor is usually found in nature on the surface of a cell. Recombinant membrane-bound and soluble GBS toxin receptors can be produced by laboratory techniques known in the art. GBS toxin receptor refers to any receptor that interacts with a GBS toxin as defined herein.

As used herein, a vaccine or method is said to "prevent" or "protect against" a medical condition if its administration to an individual results in the failure of the individual to develop the medical condition.

As used herein, a vaccine or method is said to "ameliorate," "attenuate" or "lessen the severity of" a medical condition if its administration to an individual results either in the suppression or partial suppression of at least one symptom or other manifestation of the medical condition in the individual.



As used herein, a vaccine or method is said to "decrease the incidence of" a medical condition if its administration to an individual has the effect of decreasing the probability that the individual will develop the medical condition.

A "pathoangiogenic condition" is any medical condition associated with pathological angiogenesis such as that caused by for instance the hypoxia-induced, VEGF-mediated formation of new vasculature from dedifferentiated endothelial cells. Pathological angiogenesis occurs in such diseases as diabetic retinopathy, hemangioma, cancer, psoriasis, RA, osteoarthritis and atherosclerosis. (Folkman *et al.*, *Science*, 235:442 (1987); Kimball *et al.*, *Agents & Actions*, 34:329 (1991)). It is also associated with the formation of glial scars in the vicinity of injured nerves and in the formation of keloids, reperfusion injuries and scars during wound healing. Pathological angiogenesis is distinct from physiological neovascularization, a basic repair mechanism that occurs under normal, healthy circumstances (such as wound healing, the female menstrual cycle, and pregnancy) and is believed to result from the proliferation of existing endothelial cells after the disruption of contact inhibition (Brem & Folkman, *J. Ped. Surg.*, 28:445 (1993)).

An "immune response" may be humoral or cell-mediated or both. In a humoral response, the immunized animal produces antibodies that recognize and specifically bind a particular antigen. Preferably, the titer for such antibodies would be at least about 1:200 as measured by ELISA. A cell-mediated immune response is characterized by the presence of helper T cells, suppressor T cells, and/or cytotoxic T cells that recognize the antigen. The presence of such cells can be confirmed by methods known in the art, including the development of a raised area of at least 1mm within 72 hours after the subcutaneous administration of a sample of the antigen.

As used in the context of an antibody administered to a mammal, such an antibody is "immunocompatible" with such mammal if the mammal's immune system does not treat it as a foreign protein and mount an immune response against it. The antibody to be administered may be obtained from a mammal of the same species as the recipient mammal. Alternatively, such antibody can be engineered to contain constant regions that resemble those of antibodies naturally produced by the recipient mammal. Where the recipient mammal is a human, such antibodies are frequently referred to as "humanized" antibodies.

The term "immunogenic" means having antigenic properties or being capable of being specifically bound by an antibody that can specifically bind the antigen. A substance has antigenic properties if it can generate or is capable of eliciting an immune response when

administered to an animal under conditions known in the art to facilitate the production of antibodies and/or T cells that will recognize and elicit a cytotoxic response toward cells expressing the particular antigen.

The term "adjuvant" refers to an agent used to enhance the immune response of an immunized mammal to an antigen.

The term "parenteral" as used herein includes subcutaneous injections, intraperitoneal or intramuscular injection, or infusion techniques.

The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, analogs, or glycosylated, phosphorylated or myristylated isoforms of a polypeptide sequence. Hence, native protein, fragments, analogs and glycosylated, phosphorylated and myristylated isoforms are species of the polypeptide genus.

The term "isolated" as used herein in the context of a polypeptide means a polypeptide that is no longer associated with the cell that the polypeptide is normally associated with in nature in the same manner as it is normally associated in nature, such as (1) a polypeptide free of at least some other polypeptides from the same source, (2) a polypeptide expressed by a cell from a different species, (3) a polypeptide that does not occur in nature, and (4) a polypeptide produced from cDNA, recombinant RNA, or synthetic origin or some combination thereof.

The term "naturally occurring" means found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) found in nature and which has not been intentionally modified in the laboratory is naturally occurring.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned by the BLAST computer program, share at least about 80 percent sequence identity, at least about 86 percent sequence identity, and preferably at least about 90 percent sequence identity. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of about 10 or less are preferred, with about 5 or less being more preferred. Residue positions which are not identical may differ by conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side

chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine.

The term "fragment" as used herein refers to a peptide that has an amino-terminal, internal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally occurring sequence deduced, for example, from a full-length DNA sequence. Fragments typically are at least about 3 amino acids long, preferably are about 5-10 amino acids long, more preferably are about 10-50 amino acids long, and even more preferably are more than about 50 amino acids long. Also preferred are fragments that comprise one or more extracellular domains of a GBS toxin receptor. Such fragments may also comprise portions of transmembrane and intracellular domains sufficient to maintain the polypeptide fragment in a stereochemical conformation on the surface of a cell, lipid membrane, liposome, micelle, or other lipophilic structure.

The singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The SEQ ID NOs of the nucleic acid and amino acid sequences described herein are summarized below in Table 1.

**Table 1 -- Nucleic Acid and Amino Acid Sequences**

SEQ ID NO:	Type of Sequence	Description
SEQ ID NO:1	Nucleic acid	Full-length human GBS toxin receptor (HP59)
SEQ ID NO:2	Amino acid	Full-length human GBS toxin receptor (HP59)
SEQ ID NO:3	Nucleic acid	Sheep GBS toxin receptor (SP55)
SEQ ID NO:4	Amino acid	Sheep GBS toxin receptor (SP55)

The headings provided herein describe the general topic discussed and are not intended to be exclusive of information discussed in other sections. Frequently, information, methods, compositions, and other aspects may be applicable to more than one embodiment of the invention and can be so combined.

One aspect of the present invention is a method for preventing a pathoangiogenic condition in a mammal by administering to the mammal an amount of one or more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain in the mammal an immune response to at least one of the GBS toxin receptors.

Another aspect of the present invention is a method for attenuating a pathoangiogenic condition in a mammal by administering to the mammal an amount of one or

more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain in the mammal an immune response to at least one of the GBS toxin receptors. This method may be performed at a time when the mammal does not have any symptoms of the pathoangiogenic condition. Such administration serves to lessen the severity or progression of the subsequently developed pathoangiogenic condition. When the method is performed on a mammal suffering from the pathoangiogenic condition, it will ameliorate one or more symptoms of the pathoangiogenic condition.

The aforementioned methods may be performed on any animal that expresses a GBS toxin receptor on pathological neovasculature. Preferably, such animal is a mammal that does not express the receptor on healthy tissues. It is known that human embryos and full-term newborn babies up to about 10 days old have GBS toxin receptors on their lung vasculature. Sheep, cows and cats express GBS toxin receptors on their lung vasculature shortly after birth and thereafter. Preferred recipients of this method are full-term humans older than ten days, dogs, mice, pigs, goats and horses.

In other embodiments of the invention, immunized animals receive antibodies to GBS toxin receptor or immunogenic fragments thereof, or expanded autologous T cells to GBS toxin receptor, or combinations thereof. These methods may be used to attack the vasculature in pathoangiogenic conditions. These embodiments may be used independently of each other, or in combination with the treatments disclosed herein for pathoangiogenic diseases, or in combination with other treatments for pathoangiogenic diseases used in the art.

For example, as stated earlier, it was believed that GBS toxin attacks the lungs of human neonates and binds embryonic neovasculature via receptors present on these tissues at birth. GBS toxin was subsequently found to inhibit vascularization of solid tumors and ameliorate the symptoms of other diseases. Therefore, in another embodiment of the invention, in addition to receiving at least one GBS toxin receptor or at least one immunogenic fragment thereof, immunized animals also receive GBS toxin or fragments thereof, antibodies to at least one GBS toxin receptor or immunogenic fragments thereof, or expanded autologous T cells or combinations thereof. The supplemental treatments are preferred when the animal is at high risk for or is currently suffering from a pathoangiogenic condition. GBS toxin may be obtained from CarboMed, Inc. (Brentwood, TN) or may be purified as taught in U.S. Patent Nos. 5,010,062 and 5,811,403 and WO98/14603, which are hereby incorporated by reference. For human recipients, GBS toxin is preferably administered in amounts in the range of about 5µg/kg to about 25µg/kg. Methods for administering GBS toxin for the treatment of the following

pathoangiogenic conditions are taught in the following patents which are herein incorporated by reference:

	<u>Condition(s)</u>	<u>Patent</u>
	Cancer	U.S. 5,010,062
5	Scarring	U.S. 5,858,991
	Keloids	U.S. 5,858,991
	Reperfusion injury	U.S. 5,858,991
	Atherosclerosis	U.S. 5,858,991
	Burns	U.S. 5,858,991
10	Chronic wounds	U.S. 5,858,991
	Gliososis	U.S. 5,981,508
	Rheumatoid arthritis	WO98/32452
	Psoriasis	WO98/32452

15           Antibodies to the GBS toxin receptor can be obtained by immunizing animals including rabbits, mice, goats and chickens with the GBS toxin receptor or an immunogenic fragment thereof. Monoclonal antibodies, polyclonal antibodies and variants thereof can be used. Examples of variants include, but are not limited to, single-chain (recombinant) antibodies, "humanized" chimeric antibodies, and immunologically active fragments of  
20 antibodies (e.g., Fab and Fab' fragments). The production of non-human monoclonal antibodies, e.g., murine, is well known (see, e.g., Harlow *et al.*, *Antibodies A Laboratory Manual*, Cold Spring Harbor Press, pp. 139-240, 1989). Immunocompatible antibodies are preferred to prevent the immunized animal from mounting an immune response to the GBS toxin receptor antibodies. To prepare antibodies that are immunocompatible to a human, it is desirable to transfer antigen  
25 binding regions of non-human monoclonal antibodies, e.g. the F(ab')<sub>2</sub> or hypervariable regions of murine monoclonal antibodies, to human constant regions (Fc) or framework regions by recombinant DNA techniques to produce substantially human molecules. Such methods are generally known and are described in, e.g., U.S. Pat. Nos. 4,816,397 and 4,946,778, and EP publications 173,494 and 239,400. Alternatively, one may isolate DNA sequences which code  
30 for a human monoclonal antibody or portions thereof that specifically bind to the receptor protein by screening a DNA library from human B cells according to the general protocol outlined in WO 90/14430, and then cloning and amplifying the sequences which encode the antibody (or binding fragment) of the desired specificity. These sequences may be inserted into the DNA of a

mammal in such a manner that the mammal will secrete the antibodies into its milk (Genzyme Transgenics, Framingham, MA). Such antibodies may be administered intraperitoneally or intravenously. Alternate regimens can be determined by one of skill in the art using the basic principles discussed under "Administration" below.

5           The antibodies can also be used to develop a method of targeting a cytotoxic agent for delivery to a cell that expresses a GBS toxin receptor. For example, a cytotoxic agent can be coupled to an antibody that binds a GBS toxin receptor for selective delivery to the neovasculature of a growing tumor. Such a delivery system would permit a highly concentrated, localized attack on a growing tumor, while minimizing the adverse systemic side effects  
10           encountered with most chemotherapeutics.

          The sections that follow address in greater detail the selection of immunogenic fragments of the GBS toxin receptor, the production of the receptor polypeptide, identification of other GBS toxin receptors, composition preparations, vaccine preparations, pharmaceutical compositions, administration of the compositions or vaccines, and monitoring of immune  
15           response.

#### IMMUNOGENIC PEPTIDES OF THE GBS TOXIN RECEPTOR

          One embodiment of the present invention involves the administration of one or more immunogenic fragments of a GBS toxin receptor. Preferred receptors are HP59 and SP55  
20           and preferred fragments include the Hab1, Hab2 and Hab3 peptides shown in Table 3 and used in Example 1. Preferably the mammal receives a combination of at least two immunogenic fragments and more preferably all three such fragments. Co-administration of fragments from HP59 and SP55 may be desirable to elicit a robust immune response. The immunogenic fragments may contain naturally occurring post-translation modifications such as glycosylation,  
25           myristylation or phosphorylation. Other immunogenic fragments of a GBS toxin receptor may be administered in the present invention and one of skill in the art can readily identify appropriate fragments using techniques known in the art.

          A number of methods has been developed to predict the location of immunogenically important epitopes on proteins. The outcome of the combined predictions  
30           gives a good forecast of antigenic sites. Suitable GBS toxin receptor fragments may be selected, for instance, from the most hydrophilic parts of the receptor, e.g. by applying the technique described by Hopp and Woods (T. P. Hopp and K. R. Woods (1981): *Proc. Natl. Acad. Sci. U.S.A.* 78, 3824-3828). Another suitable method for selecting immunogenic fragments is

described by Chou and Fasman (P. Y. Chou and G. D. Fasman (1987) *Advances in Enzymology* 47, 45-148). Various additional algorithms can be used to predict the antigenically important regions of the GBS toxin receptor, such as a prediction of the flexibility of the polypeptide chain (P. A. Karplus and G. E. Schultz, 1985, *Naturwissenschaften* 72, 212-213), a beta-turn probability profile (P. Y. Chou and G. D. Fasman, 1979, *Biophys. J.* 26, 367-385), the probability profiles in the 3 conformations for the sequence (Gascuel, O. and J. L. Golmard, 1988, *CABIOS* 4, 357-365), a prediction of the secondary structure of the sequence (J. Novotny and C. Auffray, 1984, *Nucleic Acids Research* 12, 243-255). Additional information on the location of relevant epitopes can be obtained using the PEPSCAN-method, developed by Geysen and Meloen (H. M. Geysen, R. H. Meloen and S. J. Barteling (1984) *Proc. Natl. Acad. Sci., U.S.A.* 81(13); 3998-4002). All of these techniques can be used to select suitable GBS toxin receptor fragments for use as immunogenic antigens in the present invention.

In addition, immunoreactive epitopes of the GBS toxin receptor can be identified by expressing DNA fragments from the GBS toxin receptor gene in suitable plasmids, such as the pEX plasmids (K. Stanley and J. P. Luzio, 1984, *EMBO J.* 3, 1429-1434, and J. G. Kusters, E. J. Jager and B. A. M. Van der Zeijst, 1989, *Nucl. Acids Res.*, 17, 8007). In this system, heterologous expression leads to the synthesis of a C-terminal extension of the cro- $\beta$ -galactosidase hybrid protein. Restriction-endonuclease sites in the GBS toxin receptor DNA sequence can be used to obtain fragments of the GBS toxin receptor gene for insertion into the pEX plasmids. pEX clones synthesizing fusion proteins derived from different overlapping regions of the GBS toxin receptor are then used for further characterization. The GBS toxin receptor fragments are purified, fractionated by polyacrylamide gel electrophoresis, and blotted to nitrocellulose membranes. These membranes are then reacted with polyclonal antibodies directed at the GBS toxin receptor. Only the fragments containing the immuno-reactive epitopes will react with these antibodies. To delineate the minimal length of the epitopes, the DNA inserts of the reactive clones can be progressively shortened by Exonuclease III digestion, or by cloning synthetic oligonucleotides encoding small overlapping parts of the GBS toxin receptor (J. G. Kusters, E. J. Jager, G. Koch, J. A. Lenstra, W. P. A. Posthumus, R. H. Meloen and B. A. M. Van der Zeijst, 1989, *J. Immunol.*, 143, 2692-2698). The epitopes can then be tested for their abilities to generate an immune response in the mammal of choice. Such testing can be performed using methods known in the art as well as methods described in the "Monitoring Immune Response" section of this application.

Using the method of Hopp and Woods via the "Antigen" program in PC/GENE, Hellerqvist and colleagues have identified three regions of SP55, shown below in Table 2, as having high hydrophilicity and as likely to be immunogenic.

**Table 2 -- High Points of Hydrophilicity in SP55**

No.	Average Hydrophilicity	Sequence
1	2.05	Glu-Glu-Gly-Ser-Asp-Arg (residues 14-19 of SEQ ID NO:4)
2	1.52	Lys-Asp-Asn-Arg-Thr-Ser (residues 75-80 of SEQ ID NO:4)
3	1.33	Arg-Ala-Pro-Arg-Ala-Glu (residues 25-30 of SEQ ID NO:4)

Hellerqvist and colleagues have successfully prepared mouse monoclonal antibodies directed to the portions of HP59 shown in Table 3 and rabbit polyclonal antibodies directed at the peptides from SP55 shown in Table 4. The rabbit polyclonal antibodies bind both SP55 and HP59 and several of the hybridomas produce monoclonal antibodies that recognize both SP55 and HP59.

**Table 3 -- Immunogenic Peptides from HP59**

<u>Peptide</u>	<u>Amino Acid Sequence</u>	<u>Size</u>	<u>SEQ ID Ref.</u>
Hab1	LARNDGEESTDRTPPL	15 aa	residues 49-63 of SEQ ID NO:2
Hab2	NTTLEDNRTSKACP	14 aa	residues 112-125 of SEQ ID NO:2
Hab3	PPRPVQPARPGGFGLSGRRSL	21 aa	residues 8-28 of SEQ ID NO:2
Hab4	LARNDGEESTDRTPPLPGAPR	28 aa	residues 49-76 of SEQ ID NO:2
	AEAAPVC		

**Table 4 -- Immunogenic Peptides from SP55**

<u>Peptide</u>	<u>Amino Acid Sequence</u>	<u>Size</u>	<u>SEQ ID Ref.</u>
p56a	APSDGEEGSDRTPLLQRAPRAEPAPVC	27 aa	residues 9-35 of SEQ ID NO:4
p55a <sup>1</sup>	LAPSDGEEGSDRTPL	15 aa	residues 8-22 of SEQ ID NO:4
p57a <sup>2</sup>	NTTAKDNRTSYECA	14 aa	residues 71-84 of SEQ ID NO:4

<sup>1</sup>Peptide p55a is a fragment of an extracellular domain of GBS toxin receptor.

<sup>2</sup>Peptide p57a is a fragment of an intracellular domain of GBS toxin receptor.



## PREPARATION OF GBS TOXIN RECEPTOR POLYPEPTIDES

The GBS toxin receptor polypeptides of the present invention may be utilized in an unmodified state. Alternatively, the polypeptides may be glycosylated, myristylated, or phosphorylated at one or more of the putative sites for such post-translational modifications. The GBS toxin receptor protein or polypeptides may be prepared as homopolymers (a multitude of identical GBS toxin receptor polypeptides coupled) or heteropolymers (one or more GBS toxin receptor polypeptides coupled to one or more different GBS toxin receptor polypeptides), or may be coupled to one or more other compounds in order to enhance immunogenicity.

In one embodiment of the invention, the GBS toxin receptor protein is naturally occurring and can be isolated from a cell extract by protein purification techniques known in the art, such as, for example, ion exchange column chromatography, high performance liquid chromatography (HPLC), reverse phase HPLC, or affinity chromatography using antibodies that recognize the GBS toxin receptor. The purified protein can be optionally lyophilized and stabilized.

In another embodiment, the GBS toxin receptor or polypeptide fragments from it can be synthesized chemically by techniques well known in the art, such as solid-phase peptide synthesis (Stewart et al., *SOLID PHASE PEPTIDE SYNTHESIS*, W.H. Freeman Co., San Francisco (1963)); Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963)). These and other methods of peptide synthesis are also exemplified by U.S. Patent Nos. 3,862,925, 3,842,067, 3,972,859, and 4,105,602. The synthesis can use manual synthesis techniques or automatically employ, for example, an Applied BioSystems 430A or 431A Peptide Synthesizer (Foster City, California) following the instructions provided in the instruction manual supplied by the manufacturer.

Alternatively, the polypeptides can be expressed using polynucleotides encoding the polypeptide(s) in operative association with an appropriate control sequence including a promoter in an expression vector suitable for expression, preferably in a mammalian cell, and also in bacterial, insect, or yeast cells. Preferably, the GBS toxin receptor polynucleotide or a fragment thereof can be expressed in a mammalian system. Such expression will usually depend on a mammalian promoter, which is any DNA sequence capable of binding mammalian RNA polymerase and initiating the downstream (3') transcription of a coding sequence (e.g. structural gene) into mRNA. Usually, a promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region typically includes an RNA polymerase binding site and a transcription initiation site.

Vectors suitable for replication in mammalian cells are known in the art, and can include viral replicons, or sequences that ensure integration of the sequence encoding PAK65 into the host genome. Suitable vectors can include, for example, those derived from simian virus SV40, retroviruses, bovine papilloma virus, vaccinia virus, and adenovirus. A suitable vector, for example, is one derived from vaccinia viruses. In this case, the heterologous DNA is inserted into the vaccinia genome. Techniques for the insertion of foreign DNA into the vaccinia virus genome are known in the art, and utilize, for example, homologous recombination. The insertion of the heterologous DNA is generally into a gene that is non-essential in nature, for example, the thymidine kinase gene (tk), which also provides a selectable marker. Plasmid shuttle vectors that greatly facilitate the construction of recombinant viruses have been described (see, for example, Mackett et al. (1984); Chakrabarti et al. (1985); Moss (1987)). Expression of the heterologous polypeptide then occurs in cells or individuals which are immunized with the live recombinant vaccinia virus.

A specific case of the above embodiment is a so-called vector vaccine in which recombinant polynucleotide are produced in the immunized animal via viral vectors. The viruses applicable for this purpose should have the ability to replicate in the animals to be immunized. These viruses, furthermore, should possess a genomic region suitable for insertion of the GBS toxin receptor protein or polypeptide gene. Suitable viruses for this purpose are for example enteral viruses such as certain adeno viruses. A particular application of the present invention is concerned with bacterial vector vaccines in which bacteria capable of colonizing the mammal (e.g. *Salmonella* bacteria) are transformed in order to enable them to express a GBS toxin receptor polypeptide in such a way that it will lead to an immunogenic response against the GBS toxin receptor.

Suitable mammalian expression vectors usually contain one or more eukaryotic transcription units that are capable of facilitating expression in mammalian cells. The transcription unit is comprised of at least a promoter element to mediate transcription of foreign DNA sequences. Suitable promoters for mammalian cells are known in the art and include viral promoters such as those from simian virus 40 (SV40) (Subramani et al., *Mol Cell. Biol.* 1:854-864, 1981), cytomegalovirus (CMV) (Boshart et al., *Cell* 41:521-530, 1985), Rous sarcoma virus (RSV), adenovirus (ADV) (Kaufman and Sharp, *Mol. Cell. Biol.* 2:1304-1319, 1982), and bovine papilloma virus (BPV), as well as cellular promoters, such as a mouse metallothionein-1 promoter (U.S. Patent No. 4,579,821), a mouse VK promoter (Bergman et al., *Proc. Natl. Acad.*

*Sci. USA* 81:7041–7045, 1993; Grant *et al.*, *Nuc. Acids Res.* 15:5496, 1987), and a mouse VH promoter (Loh *et al.*, *Cell* 33:85–93, 1983).

The optional presence of an enhancer element (enhancer), combined with the promoter elements described herein, will typically increase expression levels. An enhancer is any regulatory DNA sequence that can stimulate transcription up to 1000-fold when linked to endogenous or heterologous promoters, with synthesis beginning at the normal mRNA start site. Enhancers are also active when they are placed upstream or downstream from the transcription initiation site, in either normal or flipped orientation, or at a distance of more than 1000 nucleotides from the promoter (Maniatis *et al.* (1987) *Science* 236:1237; Alberts *et al.* (1989) MOLECULAR BIOLOGY OF THE CELL, 2nd ed.). Enhancer elements derived from viruses can be particularly useful, because they typically have a broader host range. Examples useful in mammalian cells include the SV40 early gene enhancer (Dijkema *et al.* (1985) *EMBO J.* 4:761) and the enhancer/promoters derived from the long terminal repeat (LTR) of the Rous Sarcoma Virus (Gorman *et al.* (1982b) *Proc. Natl. Acad. Sci.* 79:6777), from human cytomegalovirus (Boshart *et al.* (1985) *Cell* 41:521) as well as the mouse  $\mu$  enhancer (Gillies, *Cell* 33:717–728, 1983). Additionally, some enhancers are regulatable and become active only in the presence of an inducer, such as a hormone or metal ion (Sassone-Corsi and Borelli (1986) *Trends Genet.* 2:215; Maniatis *et al.* (1987) *Science* 236:1237).

In addition, the transcription unit can also be comprised of a termination sequence and a polyadenylation signal which are operably linked to the GBS toxin receptor coding sequence. Polyadenylation signals include, but are not limited to, the early or late polyadenylation signals from SV40 (Kaufman and Sharp), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto *et al.*, *Nuc. Acids Res.* 9:3719–3730, 1981).

Sequences that cause amplification of the gene may also be desirable, as are sequences which encode selectable markers. Selectable markers for mammalian cells are known in the art, and include, for example, thymidine kinase, dihydrofolate reductase (together with methotrexate as a DHFR amplifier), aminoglycoside phosphotransferase, hygromycin B phosphotransferase, asparagine synthetase, adenosine deaminase, and antibiotic resistant genes such as neomycin.

A GBS toxin receptor, or fragment thereof, can be expressed on the surface of a cell, or can be expressed in soluble or secreted form. Expression on the surface of the cell can be achieved, for example, by including a secretory leader operably linked to a nucleic acid sequence

encoding the desired receptor fragment and at least one transmembrane domain. The secretory leader can be that encoded by the GBS toxin receptor gene, or can be a heterologous leader sequence commonly used in the art, such as, for example, the leader sequence of *Schizosaccharomyces pombe* *pho1*<sup>+</sup> acid phosphatase (Braspenning *et al.*, *Biochem Biophys Res. Commun.* (1998) 245:166-71), the leader sequence of human interleukin-2 (IL-2) gene (Sasada *et al.*, *Cell Struct Funct* (1988) 13:129-141). Expression in soluble or secreted form can be achieved, for example, by excluding from the gene construct nucleic acid sequences encoding a transmembrane domain. In some instances, solubility and/or secretion are achieved by the use of a fusion partner, such as, for example, chloramphenicol acetyltransferase (CAT),  $\beta$ -galactosidase, and other genes readily expressed in the selected host cell.

The vector that encodes GBS toxin receptor can be used for transformation of a suitable mammalian host cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus and transducing a host cell with the virus or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. The transformation procedure used depends upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including, but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), N1E-115 (Liles *et al.*, *J. Biol. Chem.* 261:5307-5313, 1986), PC 12 human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines, such as insect derived cell lines IF9 and IF21. Cell lines of particular preference are those expressing recombinant GBS toxin receptor constructs constitutively, lines which subsequently develop characteristics of a transformed cell, and lines that more preferably express GBS toxin receptor or fragments on the cell surface. Particularly preferred are ECV cells (a bladder carcinoma cell line originally referred to in the scientific literature as an endothelial cell line), human umbilical vein endothelial cells (HUVEC), bovine, sheep, and human adrenal medulla endothelial cells.

Recombinant GBS toxin receptor or fragments thereof can be produced by culturing host cells expressing the receptor or fragment in a suitable culture medium and under appropriate cell culture conditions. Culture media and conditions are variable depending on the requirements of a particular host cell line and are well known in the art. Typically, cells are  
5 cultured at 37°C in a cell culture incubator with a fixed amount of CO<sub>2</sub>, usually in the range of 5-10%.

#### IDENTIFICATION OF OTHER GBS TOXIN RECEPTORS

In addition to the preferred GBS toxin receptors HP59 and SP55, other naturally  
10 occurring GBS toxin receptors can be used in methods, compositions and vaccines of the present invention. Nucleic acids encoding such receptors can be isolated from various tissue sources and cell cultures from different species that produce such a receptor by the methods described herein, such as, for example, cells from tumor endothelium, synovial tissue in rheumatoid arthritis, or hypoxic tissue deprived of or restricted from blood flow, such as in reperfusion injury or  
15 wounded tissue. Such polynucleotides can be isolated by hybridization using probes or by polymerase chain reaction using oligonucleotides, as well as by implementing other molecular biology techniques known in the art. Such probes and oligonucleotides typically comprise various regions of the sequence of SEQ ID NO:1 or 3, or encode various regions of the sequence of SEQ ID NO:2 or 4. Alternatively, additional target proteins for CM101 may be expression  
20 cloned. This method is described in WO 00/05375. Alternatively, subtractive hybridization between similar tissues that do and do not express the GBS toxin receptor may be used to isolate additional GBS toxin receptors. Examples of such tissues are wounded tissue and corresponding non-wounded tissue; tumor tissue and a sample of the same tissue that is free of histopathological abnormality; and lung tissue of appropriate mammals during expression of the  
25 GBS toxin receptor and shortly after expression stops. Upon discovery of an additional receptor, the probes may comprise various regions of the newly discovered receptor.

Polynucleotides useful for cloning genes encoding GBS toxin receptors of various organisms can be determined by comparing the amino acid sequences of homologous proteins. (see Table 5 which compares amino acids 41-536 of HP59 with amino acids 1-495 of SP55). For  
30 example, conserved regions can be targeted for the synthesis of oligonucleotides or degenerate oligonucleotides to be used as probes for hybridization or nucleic acid amplification, techniques discussed further below. Stringency can be varied to achieve selective hybridization conditions whereby nucleic acid sequences having less than 95% identity with respect to each other will

hybridize. These conditions are known in the art and discussed herein. Generally, the nucleic acid sequence identity between HP59 or SP55 and a nucleic acid sequence of interest will be at least about 80%, and more typically with preferably increasing identities of at least about 85% and 90%.

5 Polynucleotides can be used as probes under high stringency wash conditions and with corresponding hybridization conditions, as known in the art. Small polynucleotides, for example, polynucleotides 200 bases or fewer in length, are often referred to in the art as oligonucleotides. Techniques for using polynucleotides as probes to detect the same or related nucleic acid sequences is well known in the art. See, for example, Sambrook *et al*, especially  
10 Chapter 11. Usually, probes can be made from polynucleotides that are 10 to 200 bases in length. Preferably probes are made from polynucleotides 10 to 60 nucleotides in length and most preferably 12 to 40 bases in length. Specific probes can be designed based on results obtained using nucleic acid homology computer programs such as FASTA, which uses the method of Pearson and Lipman (*Proc. Natl. Acad. Sci. USA* 85:2444-2448 (1988)) and shows the degree of  
15 identity between compared sequences. The size of the probe is dependent upon the region of the gene to which it will be hybridized. The size of the probe increases as the degree of homology to undesirable nucleic acid sequences increases. A probe 10-50 nucleotides in length can be used, preferably more than 50 nucleotides, even more preferably more than 100 nucleotides, and most preferably a probe made from the entire coding region of a GBS toxin receptor will be used. To  
20 decrease the number of false positives, preferably two probes are used to identify clones that bind to both probes under hybridization and wash conditions. Oligonucleotides can be synthesized on an Applied BioSystems oligonucleotide synthesizer according to specifications provided by the manufacturer.

Typically, hybridization and washing conditions are performed at according to  
25 conventional hybridization procedures. Typical hybridization conditions for screening plaque lifts (Benton and Davis (1978) *Science* 196: 180) can be: 50% formamide, 5 x SSC (sodium chloride, sodium citrate) or SSPE (sodium chloride, sodium phosphate, EDTA), 1-5 x Denhardt's solution, 0.1-1% SDS, 100-200  $\mu$ g sheared heterologous DNA or tRNA, 0-10% dextran sulfate,  $1 \times 10^5$  to  $1 \times 10^7$  cpm/ml of denatured probe with a specific activity of about  $1 \times 10^8$  cpm/ $\mu$ g,  
30 and incubation at 42°C for about 6-36 hours. Prehybridization conditions are essentially identical except that probe is not included and incubation time is typically reduced. Washing conditions are typically 1-3 x SSC, 0.1-1% SDS, 42-70°C with change of wash solution at about 5-30 minutes. For high stringency hybridization conditions, various parameters can be altered to

increase the stringency of hybridization, such as by increasing the temperature of incubation with the labeled probe. Preferably, for greater flexibility in experimental design, the probe can be hybridized at a lower temperature, such as, for example, room temperature and the stringency can then be modified by altering the salt concentration and temperature of the wash solutions.

- 5 For high stringency a wash temperature of greater than or equal to 42°C can be used, such as, for example, 68°C, in a wash buffer having a salt concentration less than 3X SSC, such as, for example, 0.1X SSC. In some cases, TMACL can also be used, particularly for polynucleotides rich in G-C base pairs in order to decrease non-specific binding. A lower stringency wash can be used to hybridize polynucleotides with lower identities or polynucleotides that are less than
- 10 60 base pairs in length. For a low stringency wash, temperatures of less than or equal to 42° can be used in a wash buffer having a salt concentration of greater than or equal to 2X SSC.

**Table 5 -- Alignment of Human and Sheep GBS Toxin Receptor Amino Acid Sequences**

SP55	MKSPVSDLAPSDGEEGSDRTPLLQRAPRAEPAPVCCSARYNLAFLSFFGF	50
HP59	MRSPVRDLARNDGEESTDRTPLLPAPRAEAPVCCSARYNLAILAFFGF	91
SP55	FVLYSLRVNLSVALVDMVDSNTTAKDNRTSYECAEHSAPIKVLHNQTGKK	100
HP59	FIVYALRVNLSVALVDMVDSNTTLEDNRTSKACPEHSAPIKVHVNQTGKK	141
SP55	YRWDAETQGWILGSFFYGYIITQIPGGYVASRSGGKLLLGFGIFATAIFT	150
HP59	YQWDAETQGWILGSFFYGYIITQIPGGYVASKIGGKMLLGFGILGTAVLT	191
SP55	LFTPLAADFGVGALVALRALEGLGEGVTYPAMHAMWSSWAPPLERSKLLS	200
HP59	LFTPIAADLGVGPLIVLRALEGLGEGVTFPAMHAMWSSWAPPLERSKLLS	241
SP55	ISYAGAQLGTVVSLPLSGVICYYMNWTYVFYFFGIVGIIWFILWICLVSD	250
HP59	ISYAGAQLGTVISLPLSGIICYYMNWTYVFYFFGTIGIFWFLWILVSD	291
SP55	TPETHKTITPYEKEYILSSLKNQLSSQKSVPIWMLKSLPLWAIIVVAHFS	300
HP59	TPQKHKRISHYEKEYILSSLRNQLSSQKSVWPVILKSLPLWAIIVVAHFS	341
SP55	YNWTFYTLTLLPTYMKEVLRFNIEQENGFLSAVPYLGWLCMILSGQAAD	350
HP59	YNWTFYTLTLLPTYMKEILRFNVQENGFLSSLPYLGSWLCMILSGQAAD	391
SP55	NLRARWNFSTLWVRRVFSLIGMIGPAIFLVAAGFIGDYSLAVAFLTIST	400
HP59	NLRAKWNFSTLCVRRIFSLIGMIGPAVFLVAAGFIGDYSLAVAFLTIST	441

SP55	TLGGFCSSGFSINHLDIAPSYAGILLGITNTFATIPGMIGPIIARSLTPE	450
HP59	TLGGFCSSGFSINHLDIAPSYAGILLGITNTFATIPGMVGPVIAKSLTPD	491
SP55	NTIGEWQTVFCIAAAINVFGAIFFTLFAKGEVQNWAI SDHQGHRN	495
HP59	NTVG EWQTVFYIAAAINVFGAIFFTLFAKGEVQNWALNDHHGHRH	536

#### VACCINE PREPARATION

A preferred embodiment of the present invention is a conjugate vaccine in which the GBS toxin receptor or fragment thereof is covalently linked to a "carrier" protein or polypeptide. The linkage serves to increase the antigenicity of the GBS toxin receptor polypeptide. Methods for forming conjugate vaccines from an antigenic molecule and a "carrier" protein or polypeptide are known in the art (Jacob, C. O, *et al.*, *Eur. J. Immunol.* 16:1057-1062 (1986); Parker, J. M. R. *et al.*, In: MODERN APPROACHES TO VACCINES, Chanock, R. M. *et al.*, eds, pp. 133-138, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1983); Zurawski, V. R, *et al.*, *J. Immunol.* 121:122-129 (1978); Klipstein, F. A, *et al.*, *Infect. Immun.* 37:550-557 (1982); Bessler, W. G, *Immunobiol.* 170:239-244 (1985); Posnett, D. N, *et al.*, *J. Biol. Chem.* 263:1719-1725 (1988); Ghose, A. C, *et al.*, *Molec. Immunol.* 25:223-230 (1988)). A prototype model for conjugate vaccines was developed against *Hemophilus influenzae* (Anderson, P, *Infec. and Immun.* 39:223-238 (1983); Chu, C, *et al.*, *Infect. Immun.* 40:245-256 (1983); Lepow, M, *Pediat. Infect. Dis. J.* 6:804-807 (1987)), and this model may be employed in constructing the novel vaccines of the present invention. Additional methods for producing such a conjugate vaccine are disclosed by Anderson, P. W, *et al.*, European Patent Publication 245,045; Anderson, P. W, *et al.*, U.S. Pat. Nos. 4,673,574 and 4,761,283; Frank, R. *et al.*, U.S. Pat. No. 4,789,735; European Patent Publication No. 206,852; Gordon, L. K, U.S. Pat. No. 4,619,828; and Beachey, E. H, U.S. Pat. No. 4,284,537. Useful carriers include keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, human serum albumin, human gamma globulin, chicken immunoglobulin G, bovine gamma globulin and tetanus toxoid. Alternatively, the GBS toxin polypeptide may be conjugated or linked to immunogenic polysaccharides such as group A *Streptococci* polysaccharide, C-polysaccharide from group B *Streptococci*, or the capsular polysaccharide of *Streptococci pneumoniae*.

Another embodiment of the present invention is a whole cell vaccine in which the transfected or normal cell expressing a GBS toxin receptor on its membrane may be alive or fixed and killed.



As would be understood by one of ordinary skill in the art, when the vaccine of the present invention is provided to an individual, it may be in a composition which may contain salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same site of the mammal being immunized. Alum is a registered adjuvant for human use. Other adjuvants are being developed for human use and it is anticipated that these other adjuvants would be suitable for use in preparing compositions for human vaccination in accordance with this invention. Suitable adjuvants for the vaccination of animals include but are not limited to oil emulsions such as Freund's complete or incomplete adjuvant (not suitable for livestock use), Marcol 52: Montanide 888 (Marcol is a Trademark of Exxon. Montanide is a Trademark of SEPPIC, Paris), squalane or squalene, Adjuvant 65 (containing peanut oil, mannide monooleate and aluminium monostearate), mineral gels such as aluminium hydroxide, aluminium phosphate, calcium phosphate and alum, surfactants such as hexadecylamine, octadecylamine, lysolecithin, dimethyldioctadecylammonium bromide, N,N-dioctadecyl-N',N'-bis(2-hydroxyethyl) propanediamine, methoxyhexadecylglycerol and pluronic polyols, polyanions such as pyran, dextran sulfate, polyacrylic acid and carbopol, peptides and amino acids such as muramyl dipeptide, dimethylglycine, tuftsin and trehalose dimycolate.

The polypeptides of the present invention can also be administered following incorporation into liposomes or other micro-carriers.

#### PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions of the invention preferably include a pharmaceutically acceptable carrier that may contain a variety of components that provide a variety of functions, including regulation of drug concentration, regulation of solubility, chemical stabilization, regulation of viscosity, absorption enhancement, regulation of pH, and the like. For example, in water soluble formulations the pharmaceutical composition preferably includes a buffer such as a phosphate buffer, or other organic acid salt, preferably at a pH of between about 7 and 8. Other components may include antioxidants, such as ascorbic acid, hydrophilic polymers, such as, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, dextrans, chelating agents, such as EDTA, and like components well known to those in the pharmaceutical sciences, e.g. REMINGTON'S PHARMACEUTICAL SCIENCE, 19<sup>th</sup> edition (Mack Publishing Company, Easton, PA).

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble, alkali metal or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. Solutions of the GBS toxin receptor polypeptide as a free base or a pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of a dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the GBS toxin receptor polypeptide in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those

enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from the previously sterile-filtered solution thereof.

5           Intranasal formulations may include vehicles that neither cause irritation to the nasal mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other known substances can be employed with the subject invention. The nasal formulations may also contain preservatives such as, but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance absorption of the subject proteins by the nasal mucosa.

10           Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be presented dry in tablet form or a product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservative.

## 15           ADMINISTRATION

### ROUTE

          The polypeptides, compositions and vaccines of the present invention can be administered orally, parenterally by injection, rapid infusion, nasopharyngeal absorption (intranasopharyngeally), dermoabsorption, or rectally. They may alternatively be administered intramuscularly, or intravenously. Compositions for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, and the like.

## DOSAGE AND FREQUENCY OF ADMINISTRATION

The amount of GBS toxin receptor polypeptide to be combined with carrier, diluent, excipient and/or adjuvant to produce a single pharmaceutical composition or vaccine dosage form will vary depending upon the pathoangiogenic condition being vaccinated against, the mammal's propensity for developing such condition or the severity of such condition, the mammal to be treated and the particular time and route of administration. It will be understood, also, that the specific dose level for any particular mammal will depend upon a variety of factors including the age, body, weight, general health, sex, and diet of such mammal. Effective dosages can be readily established by one of ordinary skill in the art through routine trials establishing dose-response curves.

Many different techniques exist for the timing of the immunizations when a multiple administration regimen is utilized. It is possible to use the compositions of the invention more than once to increase the level, diversity and stability of the immune response in the immunized animal. Multiple doses may be required to maintain a state of immunity to GBS toxin receptor. If so, multiple immunizations will be given at intervals appropriate to maintain the desired immune response.

## MONITORING IMMUNE RESPONSE

It is desirable to characterize the immune response of a mammal that has received a vaccine according to the method of the present invention. Such characterization is preferably made in light of the mammal's immune response to the GBS toxin receptor and to various other standards prior to the initial administration of the receptor. Subsequent testing is performed within a reasonable period, preferably at least six weeks, after administration of the GBS toxin receptor. Such testing may be performed again at regular intervals thereafter or on an as-needed basis, depending on the mammal's condition. For instance, at the desired timepoint, a blood sample is harvested from the mammal and preserved in an appropriate manner until testing can be carried out. Preservation methods of the blood samples include separation of blood sera from other blood components, cooling or freezing, and preservation with various buffering or anti-coagulatory agents. Testing may also be performed on urine, stool, and tissue from lung, lymph nodes, spleen, bone marrow, ulcers, skin lesions and exudate and other tissues affected by the pathoangiogenic condition being tested.

The presence of antibodies in the serum (i.e. a humoral immune response to the GBS toxin receptor) may be determined by ELISA, RAST, EIA, hemagglutination inhibition,

other radioimmunoassay techniques, and latex agglutination methods and by general serological assays including white blood cell counts, measurement of total and differentiated immunoglobulin levels, including IgM, total IgG, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub> and IgG<sub>4</sub>, or other methods known to one of skill in the art. One possible method for performing an ELISA determination involves plating the GBS toxin receptor of interest onto ELISA plates. After unbound antigen is washed off the plates, excess protein reactive sites on the plates are blocked with a blocking buffer. Following removal of the blocking buffer, a dilution series of sera in PBS is added into wells of the blocked ELISA plates and incubated for one hour at 37°C. After removal of the dilution series, the plates are washed and a conjugated antibody solution in PBS (antibody is against the vaccinated species) is added to the wells of the ELISA plate, which is then incubated for one hour at 37°C. After removal of the conjugated antibody solution, the plates are washed and the appropriate chromogenic substrate is added to the wells to allow for color development. After a 30-minute incubation, color development is stopped and the absorbance readings of the wells are read on a spectrophotometer. The absorbance readings for each group at each dilution are averaged and plotted versus the reciprocal dilution. Positive and negative controls are an important part of this determination as is a comparison with the pre-immunization (baseline) testing. If antibodies can be detected at a dilution of about 1:200 or more, then the mammal has a positive immune response.

Determination of a cellular immune response may be made by methods known to those of skill in the art, including those discussed herein. The presence of T cells that recognize the GBS toxin receptor can be tested by administering a sample of the GBS toxin receptor subcutaneously and examining the skin of the mammal (preferably human) 72 hours later to see if the skin at the site of administration is raised by about 1mm or more. The size of such wheals are typically measured and can be correlated to the degree of immune response. Such a response is a positive immune response. Alternatively, a cellular immune response can be determined by such methods as measuring C-reactive protein serum levels, complement levels, including normal complement and C-3 detection, erythrocyte sedimentation rate, haptoglobin serum levels, immunoprotein levels and other protein serum levels.

A positive immune response means that the pathoangiogenic condition is prevented or attenuated. Prevention and attenuation can be demonstrated by methods known in the art, including but not limited to those discussed herein.

One method of demonstrating prevention is to administer the vaccine to or practice the method upon a group of individuals from a population that is susceptible to the

pathoangiogenic condition of interest and compare the incidence of the condition in such group with the incidence of the condition in the rest of the population that did not receive the vaccine or method. For example, humans who smoke are susceptible to lung cancer. A group from a test population of statistically matched smokers who do not have lung cancer can be given a vaccine or method of the present invention while the remainder of the test population will not receive any treatment. Both groups are monitored for lung cancer. If no members of the group that received the vaccine or method have developed lung cancer by a time when a statistically significant number of the remainder of the test population have developed the disease, then the vaccine or method can be concluded to prevent lung cancer. If cases of lung cancer develop in the treated group but do so at a statistically significant lower rate than that of the remainder of the population, the vaccine or method can be concluded to decrease the incidence of lung cancer. One of skill in the art can demonstrate prevention of other pathoangiogenic conditions by similar methods known in the art including testing of populations that are susceptible to the particular disease on account of genetic and/or environmental factors.

Support for additional aspects of the present invention and methods for making and using the invention are published in WO 00/05375.

#### EXAMPLES

##### **Example 1. Immunization with a mixture of three fragments from human GBS toxin receptor retards tumor growth.**

Peptides Hab1, Hab2 and Hab3, which are shown in Table 3, are fragments from amino terminus of HP59 that were selected as immunogens based on hydrophilicity. They were synthesized *in vitro* (Sigma-Genosis, The Woodlands, Texas) and conjugated to keyhole limpet hemocyanin (KLH), a glycoprotein which served as an adjuvant. Experimental C57 mice (n=8, four males and four females) were immunized by subcutaneous injection of 100 micrograms of a mixture of the three peptide conjugates in complete Freund's adjuvant (CFA). Two weeks, four weeks and six weeks later, each of these mice received a subcutaneous injection of 100 micrograms of this mixture in incomplete Freund's adjuvant (IFA). A final injection of 100 micrograms of this mixture in IFA was given intradermally at eight weeks. Control C57 mice (n=8) were immunized at the same times in the same manner with only KLH and Freund's adjuvant.

Experimental mice were bled from the tail vein 6 weeks after the initial immunization and every four weeks thereafter and the level of antibodies formed to the HP59 derived peptides were established by ELISA. When a positive antibody titer was obtained from all experimental mice, both control and experimental mice were challenged with tumor cells as follows: 50,000 mouse melanoma B1-6 cells or Lewis lung tumor cells were suspended in 0.6% agar and injected subdermally. The volume of the tumors was measured 6, 8, 10, 12 and 14 days after the tumor cell injections. As shown in Table 6, the melanoma tumors of immunized mice were 45% smaller than those of their control counterparts and the Lewis lung tumors of immunized mice were 38% smaller than those of their control counterparts. The results of both experiments were statistically significant. For the melanoma experiments, the paired t test for treated versus control was  $t=2.3898$  with five degrees of freedom and the one tailed  $p=0.0312$ , which is considered significant. For the Lewis lung experiments, the paired t test for treated versus control was  $t=2.9899$  with five degrees of freedom and the one tailed  $p=0.0152$ , which is considered significant.

**TABLE 6. Tumor progression (volume = # x mm<sup>3</sup>)**

Tumor Type	Day 6	Day 8	Day 10	Day 12	Day 14
Melanoma (n=4)	15.6	83.3	131.3	350.1	429.8
Control (n=4)	20.4	118.2	174.5	518.6	783.5
Lewis Lung (n=4)		36.9	70.8	144.8	194.6
Control (n=4)		68.8	119.4	178.8	315.1

#### **Example 2. Treatment of immunized mammals with CM101**

Mice immunized and challenged with tumor cells as described in Example 1 may additionally receive weekly intravenous infusions of 60µg/kg of the GBS toxin CM101 (CarboMed, Inc., Brentwood, TN) or mock injections. Tumor progression is compared in the CM101-treated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods. Additional experiments at different dose levels are conducted to determine a dose-response relationship.

#### **Example 3. Treatment of immunized mammals with immunocompatible antibodies**

Mice immunized and challenged with tumor cells as described in Example 1 may additionally receive weekly injections of 100µg of a mixture of mouse monoclonal antibodies specific for HP59 or mock injections. Such antibodies are obtained by immunizing mice with

100mg of the synthetic peptides shown in Table 3 in accordance with the methods taught in Harlow *et al.*, ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Press, pp.139-240 (1989). Tumor progression is compared in the antibody-treated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods.

- 5 Additional experiments at different dose levels are conducted to determine a dose-response relationship.

#### **Example 4. Treatment of immunized mammals with autologous T cells**

- 10 T cells may be removed from mice immunized and challenged with tumor cells as described in Example 1 and either incubated with a mixture of the Hab1, Hab2 and Hab3 peptides or mock incubated for 72 hours. The T cells are returned to each donor mouse by intravenous injection. Tumor progression is compared in the peptide-incubated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods. Additional experiments at different dose levels are conducted to determine a dose-response relationship.
- 15

#### **Example 5. Immunization with a mixture five fragments from human and sheep GBS toxin receptors retards tumor growth**

- 20 Two groups of male and female C57 mice and equal size controls were immunized with a mixture of five peptides shown in Tables 3 and 4, p56a, p55a, p57a, Hab1, and Hab2. These peptides were derived from the homologous proteins HP59 and SP55 (87%), conjugated with keyhole limpet hemocyanin (KLH) (Sigma Genosys, TX) and emulsified in complete Freund's Adjuvant (CFA), by intradermal injection in three places at the base of the tail.

- 25 The first immunization was followed two weeks and four weeks later with repeat intradermal injections of antigen KLH conjugate and incomplete Freund's Adjuvant (IFA) for the experimental group. IFA alone was given to control animals. Animals were bled after 5 weeks and shown to have antibody titer of 1:200 with optical density (O.D.) of >2.0. to one extracellular peptide based on a seven transmembrane domain (7TMD) configuration.

- 30 Lewis Lung cell suspension ( $5 \times 10^4$  cells) in 3% agar was implanted subcutaneously in seven immunized male and five immunized females. Four male and four female CFA and IFA immunized mice served as controls. The mice were observed until the



control tumors began to ulcerate at which time mice were sacrificed and tissues, including tumors, were collected.

The growth curve for the Lewis Lung tumors in C57 mice are shown in Fig. 1. The y-axis represents tumor volume and the x-axis represents the day the tumor volume was measured. Male controls are denoted by blackened diamonds, female controls are denoted by blackened circles; male immunized are denoted by clear circles and female immunized are denoted by clear diamonds. The raw data of tumor volumes from different days were recorded. A paired t-test using tumor volumes at the five last measurements shows a significant difference ( $p=0.025$ ) in the average tumor volumes for the non-immunized male and female with the average for the immunized groups. The overall tumor burden in the immunized mice was only 38.3% of the control.

#### **Example 6. Retardation of melanomas in female mammals**

Five each of HP59/CFA and CFA immunized, female C57 mice were inoculated intravenously with 1,000 melanoma cells. Time to death was the endpoint. Mice were to be sacrificed when respiratory distress was obvious.

The five female controls died on days 46, 52, 54, 62 and 100. The autopsy of the diseased control mice showed lungs to be infiltrated by numerous metastasis. One immunized female died early with no sign of tumors. The remaining four immunized mice were all alive at day 140 with no signs of disease, at which time two of them were inoculated with an additional 1,000 melanoma cells (denoted by an arrow in Fig. 2). The remaining four immunized mice continued to show no signs of disease on day 305. Fig. 2 shows survival curves for the female mice challenged intravenously with 1000 melanoma cells. The y-axis represents percentage of survivors and the x-axis represents the number of days of survival. The blackened circles denote female controls and the blackened squares denote female immunized mammals.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patents or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

## WHAT IS CLAIMED IS:

1. A method of preventing a pathoangiogenic condition in a mammal comprising:  
administering to said mammal an amount of one or more GBS toxin receptors or  
immunogenic fragments thereof effective to induce or maintain an immune response to at least  
5 one of the GBS toxin receptors.
2. A method of attenuating a pathoangiogenic condition in a mammal comprising:  
administering to said mammal an amount of one or more GBS toxin receptors or  
immunogenic fragments thereof effective to induce or maintain an immune response to at least  
10 one of the GBS toxin receptors.
3. The method of claim 1 or 2, wherein the pathoangiogenic condition is selected  
from the group consisting of cancer, scarring during wound healing, gliosis during repair of  
nerve injury, chronic wounds, keloids, reperfusion injury, rheumatoid arthritis, atherosclerosis,  
15 osteoarthritis and psoriasis.
4. The method of claim 1 or 2, wherein at least one GBS toxin receptor has  
substantial identity to SEQ ID NO:2.
- 20 5. The method of claim 4, wherein at least one GBS toxin receptor is identical to  
SEQ ID NO:2, or is SEQ ID NO:2 with at least one conservative amino acid substitution.
6. The method of claim 1 or 2, wherein at least one immunogenic fragment has  
substantial identity to a portion of SEQ ID NO:2.
- 25 7. The method of claim 6, wherein at least one immunogenic fragment has  
substantial identity to Hab1, Hab2, Hab3 or Hab4.
8. The method of claim 1 or 2, wherein at least one GBS toxin receptor has  
30 substantial identity to SEQ ID NO:4.
9. The method of claim 8, wherein at least one other GBS toxin receptor has  
substantial identity to SEQ ID NO:2.

10. The method of claim 8, wherein at least one GBS toxin receptor is identical to SEQ ID NO:4, or is SEQ ID NO:4 with at least one conservative amino acid substitution.

5 11. The method of claim 1 or 2, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:4.

12. The method of claim 11, wherein each of two or more immunogenic fragments has substantial identity to a portion of SEQ ID NO:4.

10

13. The method of claim 11, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:2.

14. The method of claim 12, wherein at least one immunogenic fragment has  
15 substantial identity to p55a, p56a or p57a.

15. The method of claim 1 or 2, wherein the normal tissue of the mammal does not contain the GBS toxin receptor.

20 16. The method of claim 1 or 2, wherein the administering is via a method selected from the group consisting of oral ingestion, nasal inhalation, subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection or rectal application.

17. The method of claim 2, wherein the mammal does not have the pathoangiogenic  
25 condition at the time of the administering step.

18. The method of claim 2, wherein the mammal has a pathoangiogenic condition at the time of the administering step.

30 19. The method of claim 2, further comprising administering to said mammal an amount of GBS toxin sufficient to induce a response.

20. The method of claim 19, wherein the amount of GBS toxin is at least about 5  $\mu\text{g/kg}$ .
21. The method of claim 20, wherein the amount of GBS toxin is at least about 15  $\mu\text{g/kg}$ .
22. The method of claim 21, wherein the amount of GBS toxin is at least about 20  $\mu\text{g/kg}$ .
23. The method of claim 2, further comprising administering an effective amount of one or more immunocompatible antibodies that bind to a GBS toxin receptor.
24. A method of preventing or attenuating a pathoangiogenic condition in a mammal comprising:  
administering to said mammal immunocompatible antibodies that bind to a GBS toxin receptor.
25. The method of claim 23 or 24, wherein each immunocompatible antibody is a monoclonal antibody.
26. The method of claim 23 or 24, wherein each immunocompatible antibody is obtained from a polyclonal serum.
27. The method of claim 23 or 24, wherein at least some of the immunocompatible antibodies further comprise a cytotoxic agent.
28. The method of claim 2, further comprising removing T cells from the mammal, culturing the T cells with a GBS toxin receptor, and returning the T cells to the mammal.
29. A composition comprising one or more GBS toxin receptors or immunogenic fragments thereof.

30. The composition of Claim 29 wherein the one or more GBS toxin receptors or immunogenic fragments thereof are in an amount effective for protecting against or attenuating a pathoangiogenic condition.

5 31. The composition of Claim 30 further comprising a pharmaceutically acceptable excipient.

32. The composition of claim 30, wherein at least one of the GBS toxin receptors or fragments thereof is isolated.

10

33. The composition of claim 30, further comprising an adjuvant.

34. The composition of claim 33, wherein said adjuvant is selected from the group consisting of: a water in oil composition, Freund's adjuvant, QS21, IL-12 and interferon gamma.

15

35. The composition of claim 32, wherein one of the isolated GBS toxin receptors or fragments thereof is conjugated or linked to a protein carrier.

20

36. The composition of claim 35, wherein the protein carrier is a molecule selected from the group consisting of keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, human serum albumin, human gamma globulin, chicken immunoglobulin G, bovine gamma globulin and tetanus toxoid.

25 37. The composition of claim 30, wherein at least one of the GBS toxin receptors or fragments thereof is glycosylated.

38. The composition of claim 30, wherein at least one isolated GBS toxin receptor or fragment thereof is recombinant or synthetic.

30 39. The composition of claim 30, wherein the pathoangiogenic condition is selected from the group consisting of cancer, scarring during wound healing, gliosis during repair of nerve injury, chronic wounds, keloids, reperfusion injury, rheumatoid arthritis, atherosclerosis, osteoarthritis and psoriasis.

40. The composition of claim 30, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:2.

41. The composition of claim 40, wherein at least one GBS toxin receptor is identical to SEQ ID NO:2, or is SEQ ID NO:2 with at least one conservative amino acid substitution.

42. The composition of claim 40, wherein at least one other GBS toxin receptor has substantial identity to SEQ ID NO:4.

43. The composition of claim 30, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:2.

44. The composition of claim 43, wherein at least one immunogenic fragment has substantial identity to Hab1, Hab2, Hab3 or Hab4.

45. The composition of claim 30, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:4.

46. The composition of claim 45, wherein at least one GBS toxin receptor is identical to SEQ ID NO:4, or is SEQ ID NO:4 with at least one conservative amino acid substitution.

47. The composition of claim 30, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:4.

48. The composition of claim 47, wherein at least one immunogenic fragment has substantial identity to p55a, p56a or p57a.

49. The composition of claim 30, further comprising an effective amount of one or more immunocompatible antibodies that bind to a GBS toxin receptor.

50. A composition comprising:  
antibodies that bind to a GBS toxin receptor.

51. The composition of claim 49 or 50, wherein each antibody is a monoclonal antibody.

5 52. The composition of claim 49 or 50, wherein each antibody is obtained from a polyclonal serum.

53. The composition of claim 49 or 50, wherein at least one of the antibodies further comprises a cytotoxic agent.

10

54. The composition of claim 30, further comprising T cells from the mammal that have been cultured with a GBS toxin receptor.

55. A method of producing a composition for treatment and/or prevention of  
15 pathoangiogenic conditions comprising:

providing at least one GBS toxin receptor or immunogenic fragment thereof; and  
formulating the receptor or fragment in a pharmaceutically acceptable excipient.

56. The method of claim 55 further comprising providing an adjuvant.

20

57. A method of eliciting an immune response in an animal comprising:  
administering to said mammal an amount of one or more GBS toxin receptors or  
immunogenic fragments thereof effective to induce or maintain an immune response to at least  
one of the GBS toxin receptors.

25

58. The method of claim 57 wherein the one or more immunogenic fragment is  
chosen from the group comprising residues 14-19 of SEQ. ID NO:4, residues 75-80 of SEQ. ID  
NO:4, residues 25-30 of SEQ. ID NO:4, Hab1, Hab2, Hab3, Hab4, p56a, p55a, and p57a.

30

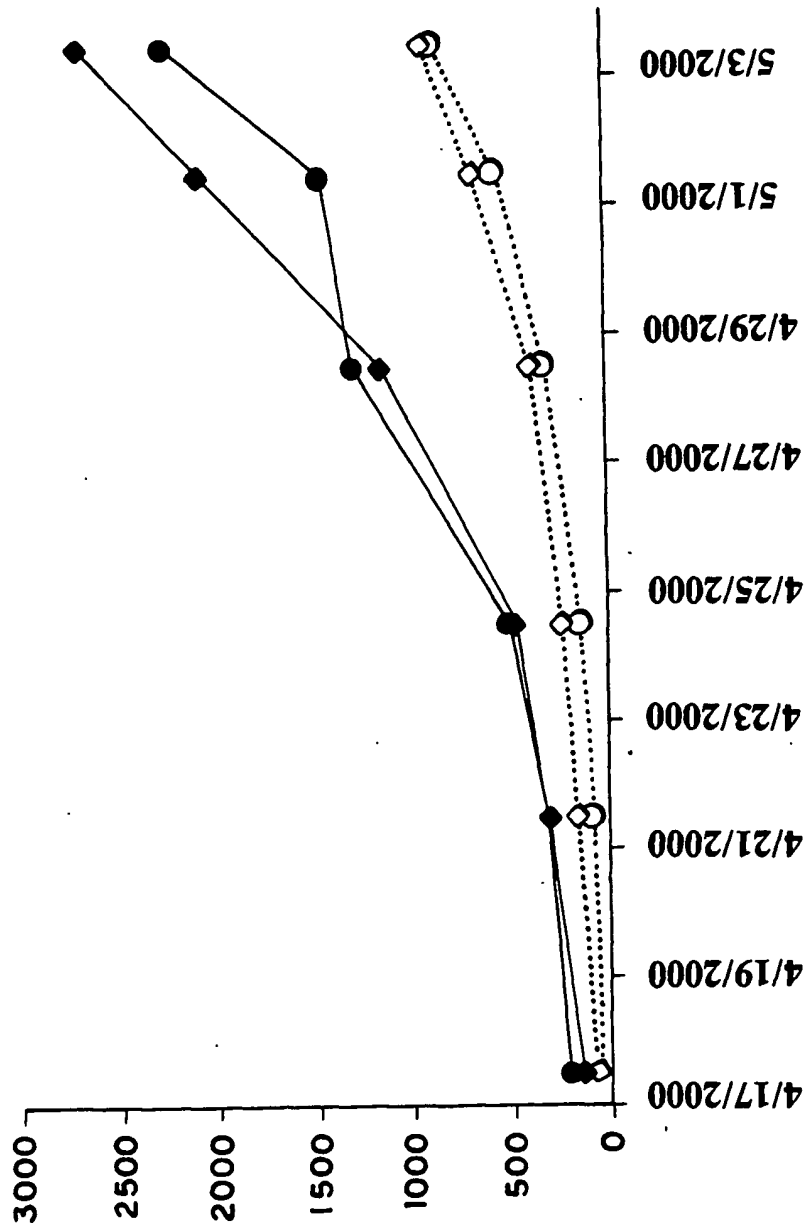
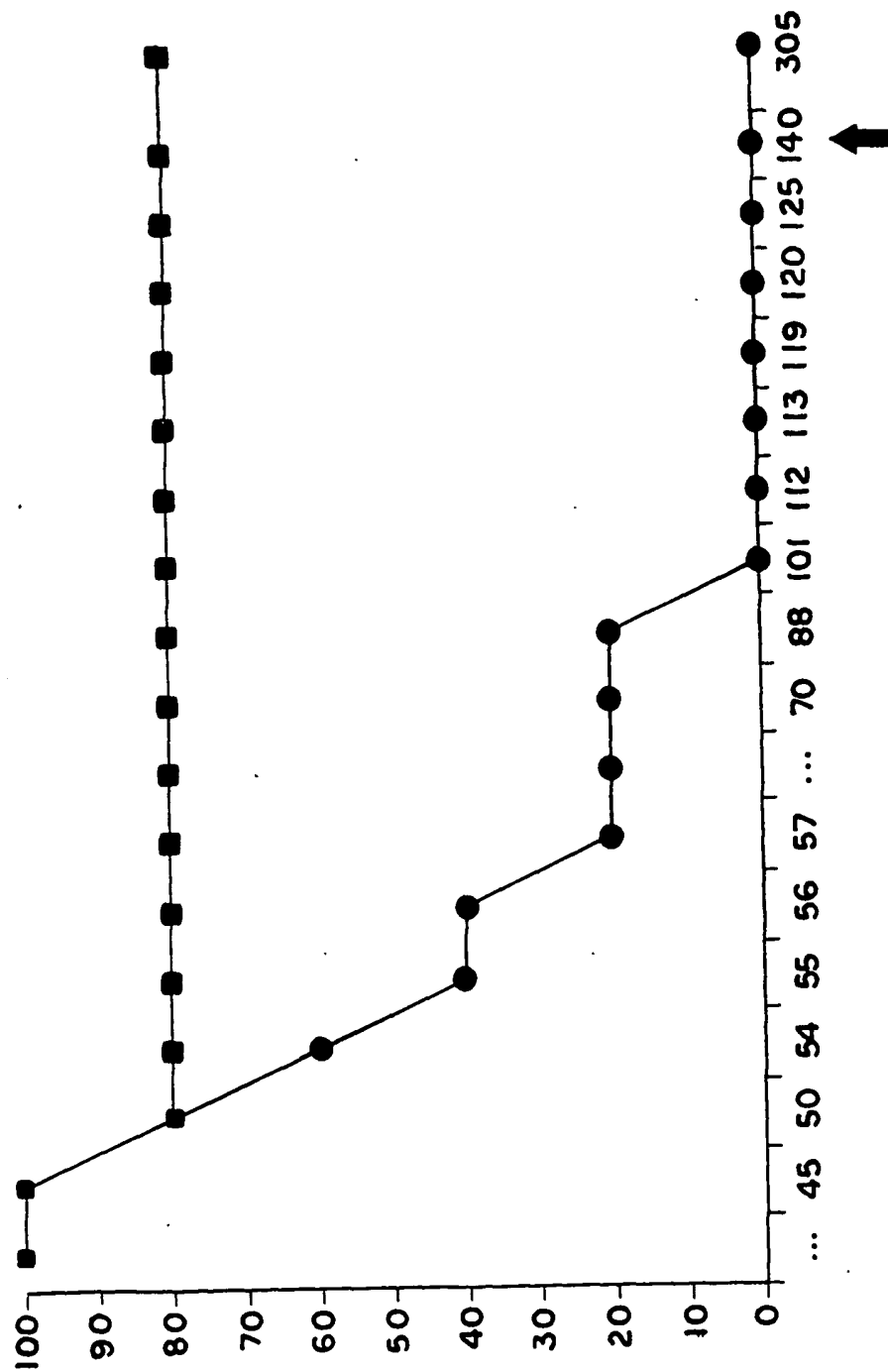


Fig-1





**Fig - 2**

## SEQUENCE LISTING

<110> Vanderbilt University

<120> Methods for Preventing or Attenuating Pathoangiogenic Conditions

<130> 22100-0100 WP 46126-252654

<150> US 60/179,870

<151> 2000-02-02

<160> 4

<170> PatentIn version 3.0

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(12) **United States Patent**  
**Hoff**

(10) Patent No.: **US 6,948,783 B2**  
(45) Date of Patent: **Sep. 27, 2005**

(54) **TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE**

(75) Inventor: **Brian D. Hoff**, East Peoria, IL (US)

(73) Assignee: **Caterpillar Inc**, Peoria, IL (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 276 days.

(21) Appl. No.: **10/067,204**

(22) Filed: **Feb. 7, 2002**

(65) **Prior Publication Data**

US 2003/0122421 A1 Jul. 3, 2003

**Related U.S. Application Data**

(60) Provisional application No. 60/342,370, filed on Dec. 27, 2001.

(51) Int. Cl.<sup>7</sup> ..... **B60B 55/30**

(52) U.S. Cl. .... **305/144; 305/145**

(58) Field of Search ..... **305/143, 144, 305/145, 153**

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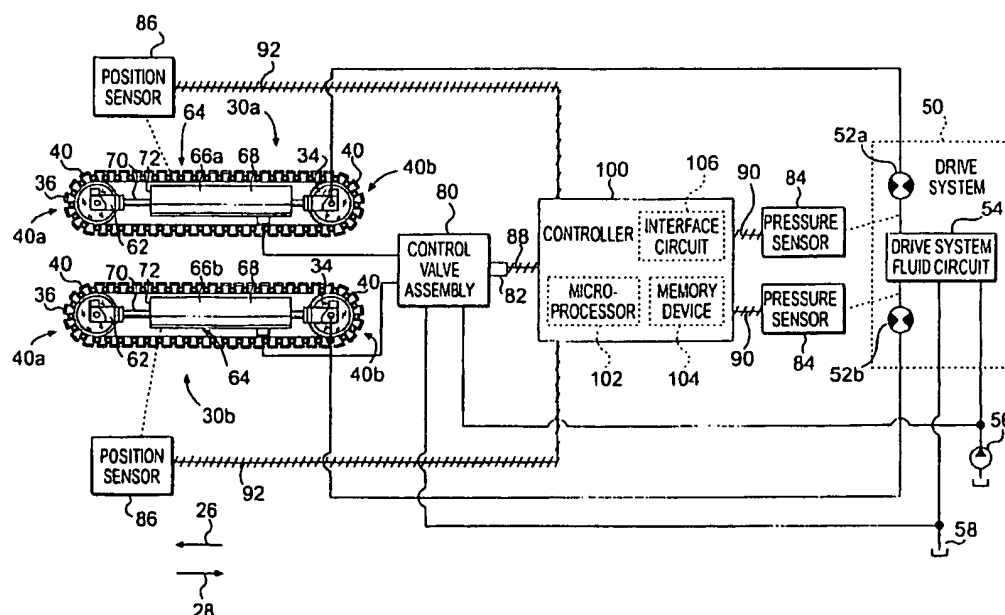
*Primary Examiner*—Russell D. Stormer

(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner

(57) **ABSTRACT**

A method of operating a track-type machine having a drive wheel and an idler. The method includes operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine. The method further includes determining a force to be applied to the idler based on a direction of operation of the drive wheel and applying the force to the idler. The method may include varying the force applied to the idler as a function of a drawbar load of the machine. The method may include sensing a pressure of fluid being used to operate the drive wheel, wherein the force is determined based on the sensed pressure of fluid being used to operate the drive wheel. The method may include determining a force to be applied to the idler by selecting a recoil curve, sensing a position of the idler, and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve. The recoil curve may be selected from a plurality of recoil curves.

**20 Claims, 5 Drawing Sheets**



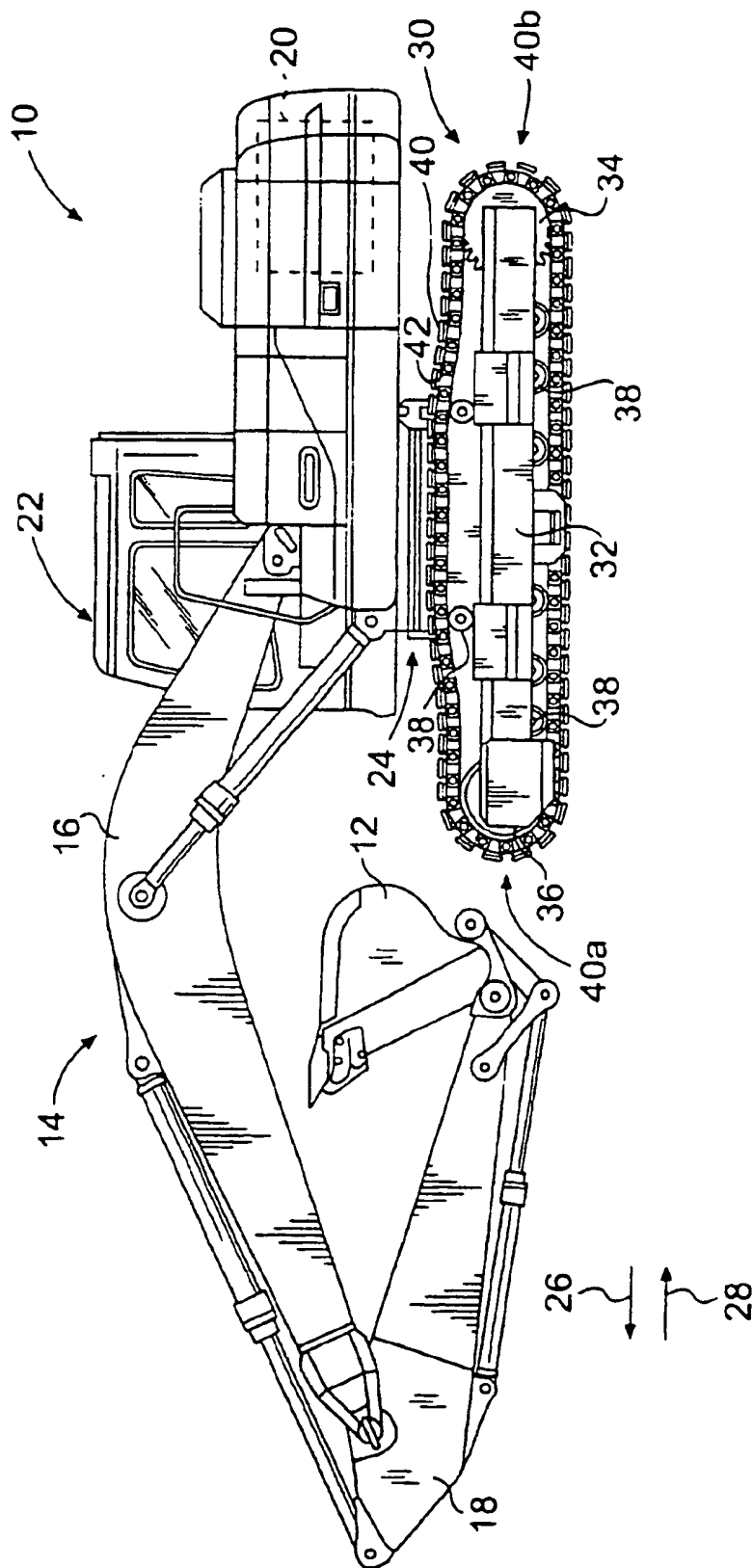


FIG. 1

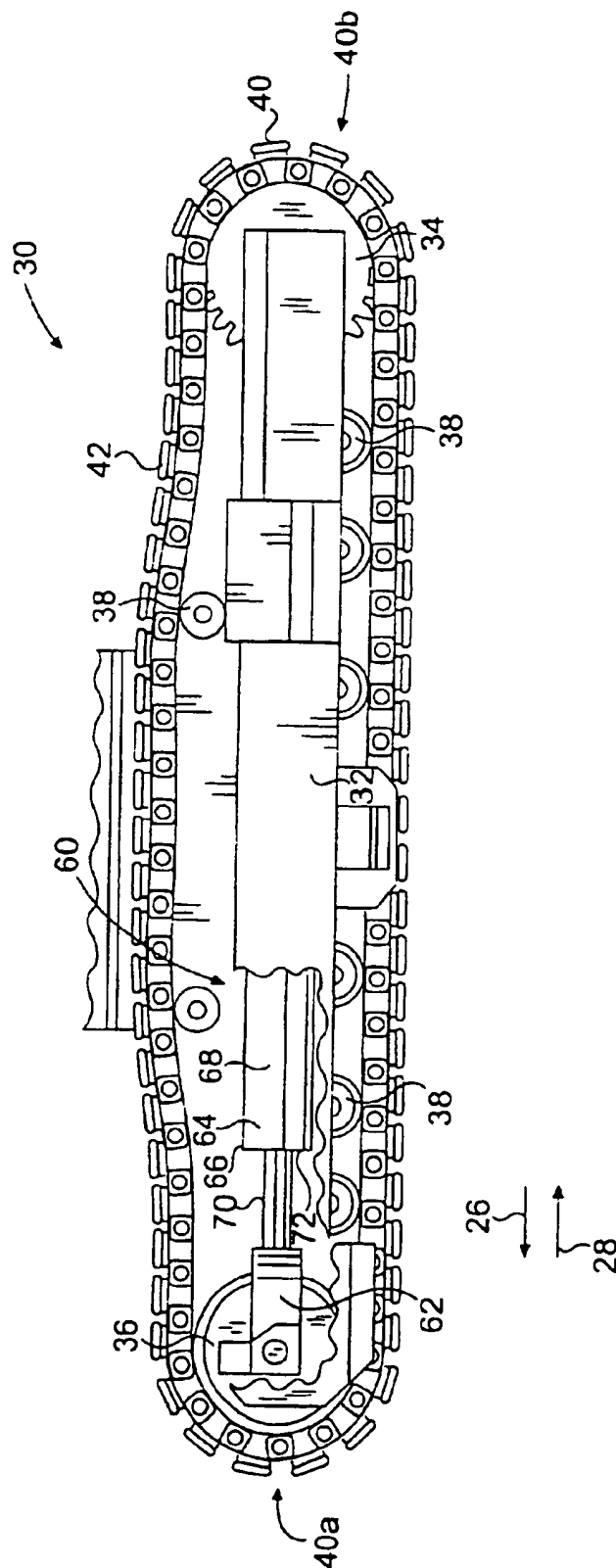


FIG. 2



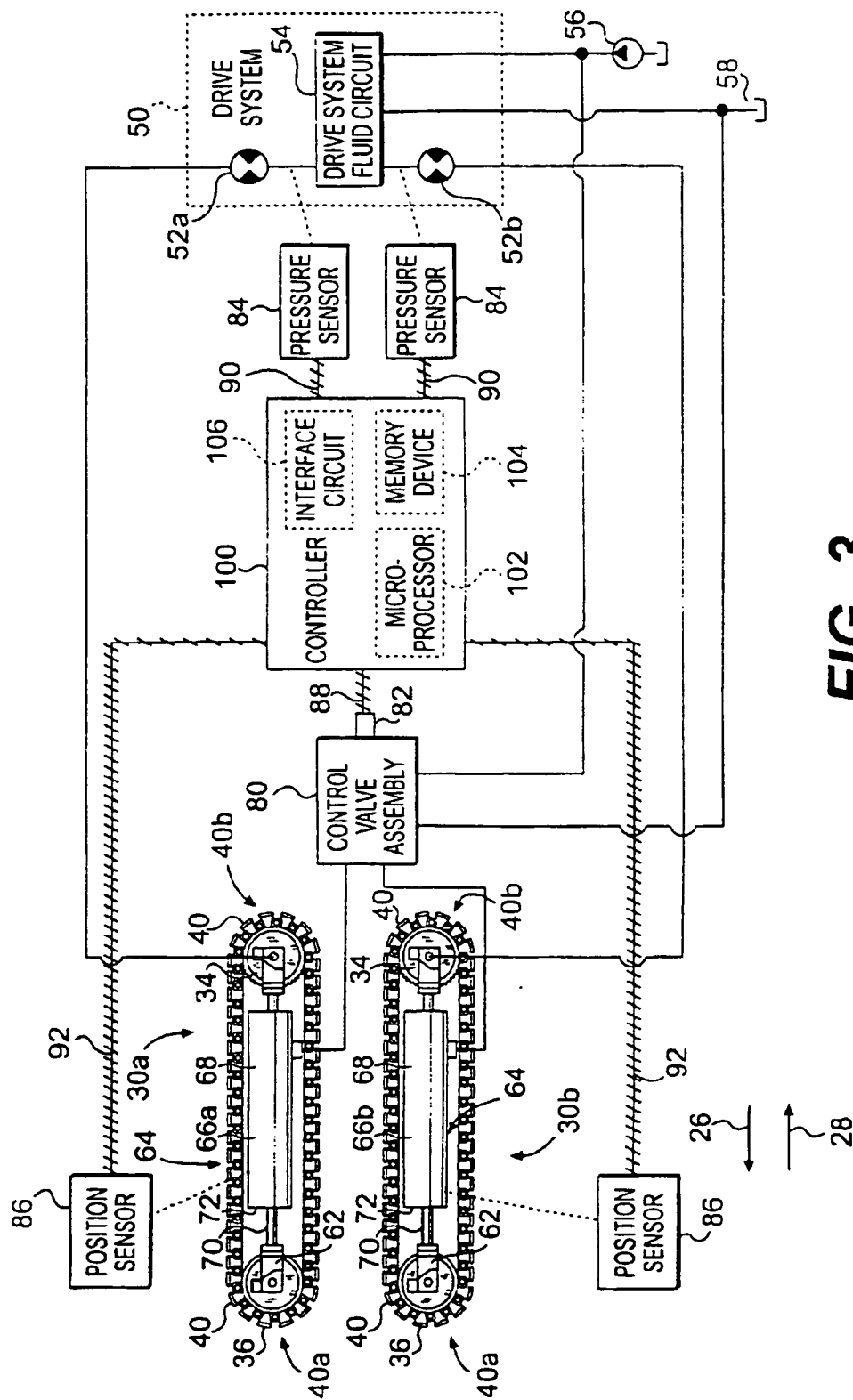


FIG. 3

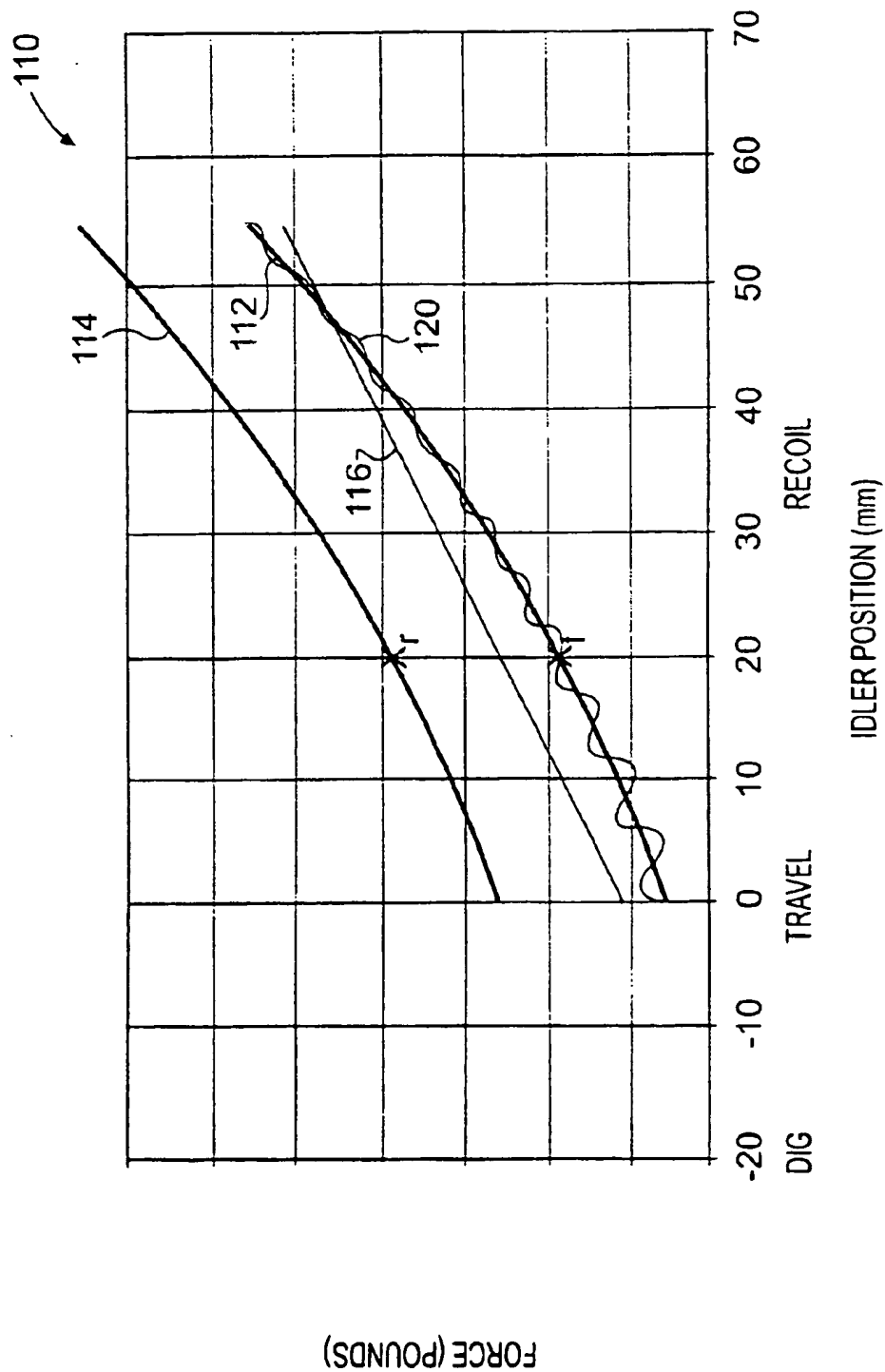
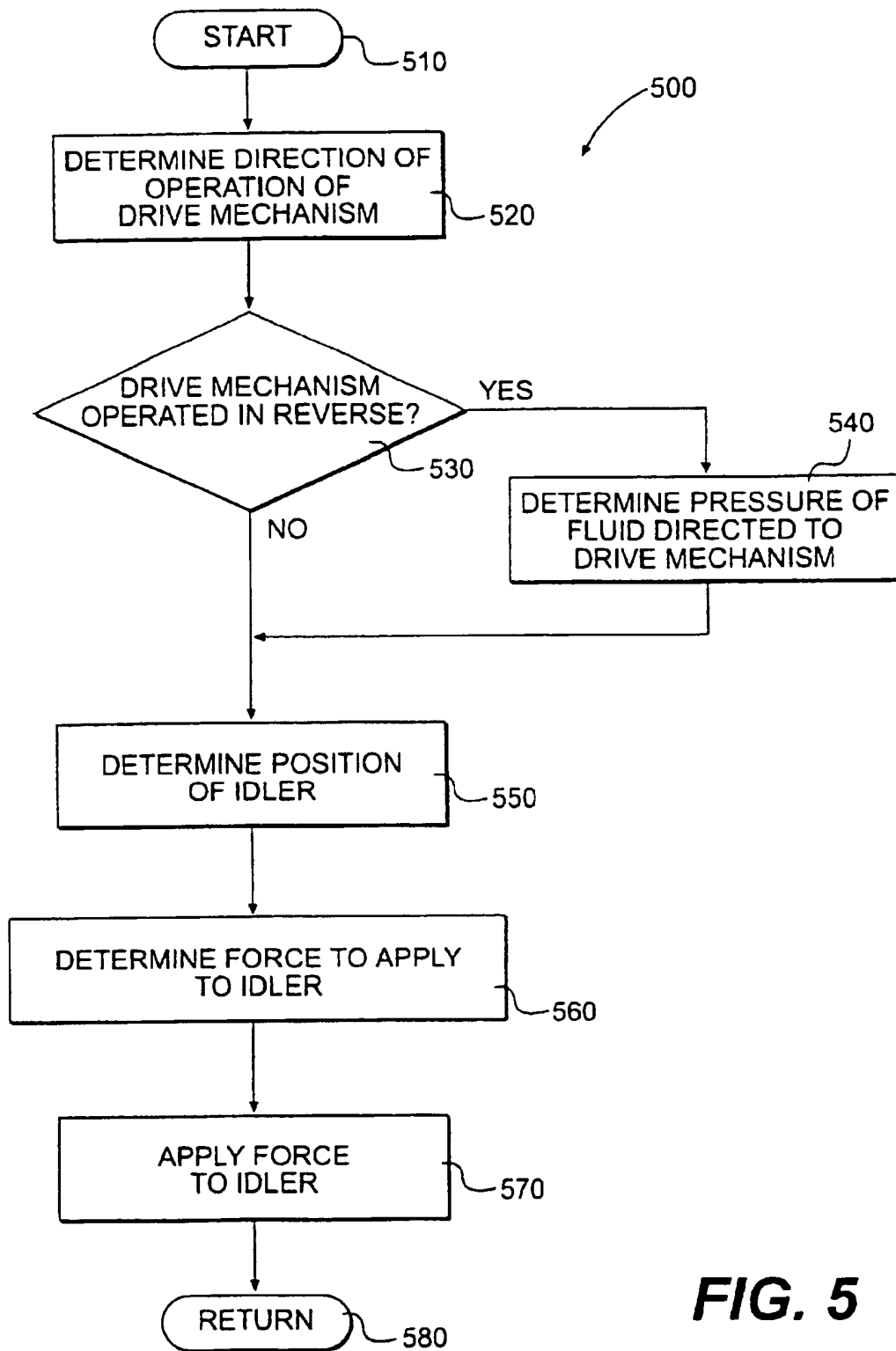


FIG. 4

**FIG. 5**

## TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE

The present application claims priority to U.S. Provisional Application Ser. No. 60/342,370, filed Dec. 27, 2001, entitled TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE, with inventor of Brian D. Hoff, which is incorporated herein by reference.

### TECHNICAL FIELD

This invention relates generally to a tension adjustment mechanism for a tracked work machine and, more particularly, to a method of providing a variable force to the idler of the machine based on the direction of operation.

### BACKGROUND

A work machine, such as a track-type tractor or excavator, is typically supported and propelled by a pair of undercarriage assemblies. Each of the pair of undercarriage assemblies includes an endless track chain having a plurality of interconnected articulating components or links. Each undercarriage assembly typically also includes a drive wheel or sprocket and one or more idler wheels. The track chain is advanced around the drive sprocket and the one or more idler wheels.

During operation of the work machine, it is necessary to maintain tension on the track chain in order to keep the chain from derailing from the drive wheel or sprocket or the idler wheel. In order to maintain tension on the track chain, a tension adjustment mechanism such as a hydraulic cylinder or coiled spring is often included in the undercarriage assembly.

With regard to excavators, it is generally desirable to have the track chain relatively taut during performance of a digging or other type of work operation in order to prevent wear on the components associated with the undercarriage assembly and to provide a more stable work platform. A relatively taut track chain helps prevent the excavator from rolling back and forth within the interior of the track chain as a result of recoil forces generated during performance of the work operation. Hence, a relatively high tension level is desirably maintained on the track chains of excavators during a work operation, even though it is known that use of such a high tension level increases the rate at which components associated with the undercarriage assembly wear, especially during travel. To create tension on the track chain, the hydraulic cylinder or the coiled spring of the tension adjustment mechanism urges the idler wheel away from the drive wheel or sprocket, increasing the dimension of the undercarriage assembly which the track chain must encircle.

In contrast, it is generally desirable to have the track chain relatively loose during advancement or travel of an excavator. By loosening or otherwise decreasing tension on the track chain, wear on the components associated with the undercarriage assembly is reduced. This increases the efficiency and even the useful life of the excavator. To reduce tension in the track chain, the hydraulic cylinder or coiled spring of the tension adjustment mechanism moves the idler wheel toward the drive wheel or sprocket a certain incremental amount.

The tension adjustment mechanism also provides a recoil function in the track chain, accommodating temporary forces on the track such as when a rock or the like is ingested between the track and the wheels during advancement of the excavator. In these instances, the idler wheel is permitted to recoil toward the drive sprocket in order to accommodate the

extra length the track must encircle in order to accommodate the rock without breaking.

When traveling in one direction, the rotation of the drive wheel or sprocket pulls on the top flight of the track chain, exerting a recoil force on the idler wheel. During travel in the opposite direction, the drive wheel or sprocket pulls on the bottom flight of the track chain which, because the bottom flight bears the weight of the machine against the ground, does not significantly transmit that force through the track chain to the idler wheel. Conventional track tension/recoil systems have a tensioning mechanism for varying track tension based on dig and travel requirements, and accordingly are not optimized for either.

U.S. Pat. No. 6,249,994 ("the '994 patent") discloses a tensioning mechanism which decreases track tension by a predetermined amount when the machine is traveling. The '994 patent discloses detecting an increase in drive pressure when the machine goes into its travel mode (because fluid is diverted from a work implement to the drive system) and then decreasing tension on the track chain in response to the detection of the increase in fluid drive pressure. Conversely, the '994 patent discloses detecting a decrease in drive pressure when the machine goes into its work mode (because fluid is diverted from the drive system to the work implement) and then increasing tension on the track chain in response to the detection of the increase in fluid drive pressure. The '994 patent does not disclose, however, differentiating between directions of travel and the drive force required to achieve travel.

In addition, conventional work machines do not effectively compensate for the advancement of the excavator under high drawbar loads, which is a common cause of "sprocket jumping," a condition where a bushing on the track chain slips over a tooth on the drive sprocket. Sprocket jumping has a detrimental effect on the wear of the components of the undercarriage assembly and on the hydraulic drive motor as it reflects large spikes in the pressure going into the drive motor. In addition, the recoil force created by the drive sprocket on the idler wheel during travel in one direction increases in proportion to the energy required to move the machine (referred to as drawbar load), sometimes moving the idler wheel too close to the drive sprocket under high drawbar loads.

The present invention is directed to solving one or more of the problems or disadvantages set forth above of current work machines.

### SUMMARY OF THE INVENTION

The present invention provides a method of operating a track-type machine having a drive wheel and an idler. The method includes operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine. The method further includes determining a force to be applied to the idler based on a direction of operation of the drive wheel and applying the force to the idler. The method may include varying the force applied to the idler as a function of a drawbar load of the machine. The method may include sensing a pressure of fluid being used to operate the drive wheel, wherein the force is determined based on the sensed pressure of fluid being used to operate the drive wheel. The method may include determining a force to be applied to the idler by selecting a recoil curve, sensing a position of the idler, and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve. The recoil curve may be selected from a plurality of recoil curves.

The present invention also provides a work machine that includes a source of pressurized fluid, a fluid reservoir, a drive track, an idler, a drive wheel, an actuator, a valve assembly, and a controller. The drive wheel is operable to advance the drive track around the drive wheel and the idler. The actuator is mechanically coupled to the idler and is operable to increase and decrease a force being applied to the idler. The valve assembly is operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir. The controller is configured to operate the valve assembly to apply a force to the idler based on a direction of operation of the drive wheel.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side elevational view of an excavator which incorporates an exemplary embodiment of the present invention therein;

FIG. 2 is an enlarged, partially cutaway side elevational view of the undercarriage assembly of the excavator of FIG. 1;

FIG. 3 is a schematic illustration of a track tensioning assembly according to an exemplary embodiment of the present invention;

FIG. 4 is a graph illustrating the recoil response of an exemplary embodiment of the present invention; and

FIG. 5 is a block diagram illustrating a method of determining a force to be applied to an idler of a track-type work machine based on the direction of operation of the machine according to the present invention.

### DETAILED DESCRIPTION

The invention as described below is applied to a hydraulic excavator. It should be appreciated that the present invention may be applied to any type of work machine having an endless track, such as a rubber belt or drive track chain, including, for example, track-type tractors, loaders, and military vehicles.

FIG. 1 illustrates a track-type work machine, for example, a hydraulic excavator 10, that is utilized to perform numerous work functions, such as digging and material movement. The excavator 10 may include a number of work implements, such as, for example, a hydraulically-powered bucket assembly 12, which is secured to an end of a boom assembly 14 having a boom arm 16 and a stick assembly 18. The excavator 10 further includes an engine such as, for example, a diesel engine 20, for providing the motive power for both advancing the excavator 10 and operating the bucket assembly 12 and the boom assembly 14.

The excavator 10 also includes a pair of undercarriage assemblies 30 (see FIG. 3), although only one undercarriage assembly 30 is shown in FIGS. 1 and 2. Each undercarriage assembly 30 generally includes a frame assembly 32, a drive mechanism 34, an idler wheel 36, and a number of midroller assemblies 38. For each undercarriage assembly 30, a drive track 40, such as, for example, an endless track chain, may be driven by the drive wheel 34 so as to be advanced around the idler wheel 36 and each of the midroller assemblies 38, thereby providing the motive power for advancing the excavator 10. It should be appreciated that drive mechanism 34 may comprise a drive wheel which is frictionally engaged with the drive track 40 or a drive sprocket which is mechanically engaged with the drive track chain 40. In one embodiment, the drive wheel 34 is positioned at a first end 40b of the assembly 30, while the idler wheel 36 is positioned at a second and opposite end 40a of the assembly 30.

As shown in FIG. 1, in an exemplary embodiment, the idler wheel 36 is positioned at the "front" end of the excavator 10 relative to a cab 22 (discussed below), while the drive wheel 34 is positioned at the "rear" end of the excavator 10 relative to the cab 22.

FIG. 3 is a schematic illustration of a track tensioning assembly according to an exemplary embodiment of the present invention. To advance the excavator 10, mechanical output from the engine 20 (see FIG. 1) is transmitted to the drive wheels 34 via a hydraulic drive system 50 having one or more hydraulic drive motors 52. Each hydraulic drive motor 52 drives at least one of the drive wheels 34 to advance the drive track 40 and, hence, the excavator 10. As shown in FIG. 3, hydraulic drive motor 52a drives a drive wheel 34 associated with one undercarriage assembly 30a and hydraulic drive motor 52b drives a second drive wheel 34 associated with the other undercarriage assembly 30b. Through a drive system fluid circuit 54, each hydraulic motor 52a, 52b of the hydraulic drive system 50 is fluidly coupled with at least one source of pressurized fluid 56, such as, for example, a high-pressure pump (see FIG. 3). The drive system fluid circuit 54 supplies pressurized hydraulic fluid to the hydraulic motors 52a, 52b.

As shown in FIG. 1, the excavator 10 also includes the cab 22 that is provided to enclose or otherwise house the devices associated with the excavator 10, which are utilized by an operator during operation of the excavator 10. In particular, the cab 22 houses an operator seat (not shown) and a number of control devices such as a control lever assembly (not shown) and a foot pedal assembly (not shown). The cab 22 is positioned on the undercarriage assembly 30 of the excavator 10 on a swivel 24. The swivel 24 allows the cab 22 to be turned in both the clockwise and counterclockwise directions relative to the pair of undercarriage assemblies 30a, 30b (see FIG. 3).

In addition to the engine 20, other components of the excavator 10 may be positioned above the swivel 24. In one embodiment, the at least one fluid source 56 may be positioned above the swivel 24. In another embodiment, one or more return tanks or fluid reservoirs 58 (see FIG. 3) may be positioned above the swivel 24. As shown in FIG. 3, in an exemplary embodiment, a single fluid source 56 and a single reservoir 58 are fluidly coupled with both the drive system 50 that supplies hydraulic fluid to the motors 52a, 52b and a control valve assembly 80 (discussed below) that supplies hydraulic fluid to a recoil assembly 64 (discussed below) of each of the undercarriage assemblies 30a, 30b. One skilled in the art understands that the components positioned above the swivel 24 are connected with the components of the undercarriage assembly 30 through various conventional fluid and electrical lines (not shown) that travel through the swivel 24 or through wireless communications (such as a radio) (not shown). Typically, the hydraulic motors 52a, 52b of the hydraulic drive system 50 (not shown in FIG. 1) are positioned below the swivel 24.

As shown in more detail in FIG. 2, each undercarriage assembly 30 includes a track tensioning assembly 60. The track tensioning assembly 60 is configured to (1) provide a relative taut track configuration in order to minimize wear and prevent the excavator 10 from rolling back and forth during a work operation and (2) loosen the tension on the drive track 40 during advancement of the excavator 10 in order to decrease undercarriage component wear.

The track tensioning assembly 60 includes a recoil assembly 64 having a yoke 62 secured thereto. As shown in FIGS. 2 and 3, the idler wheel 36 is rotatably coupled to the yoke

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62. Movement of the yoke 62 and hence the idler wheel 36 away from the drive wheel 34 (i.e., in the general direction of arrow 26 of FIGS. 1-3) increases tension of the drive track 40. Conversely, movement of the yoke 62 and hence the idler wheel 36 toward the drive wheel 34 (i.e., in the general direction of arrow 28 of FIGS. 1-3) decreases tension of the drive track 40.

The recoil assembly 64 includes an actuator that generally includes a cylinder that defines a chamber or housing, and a rod and/or a piston that are positioned within the housing. The components of the recoil assembly 64 are assembled together such that one component is fixed to the frame assembly 32 of the undercarriage assembly 30, while another component is moveable relative to the first component and is connected with the idler wheel 36 (through the yoke 62 as noted above) so as to urge that idler wheel 36 to increase and decrease tension on the drive track 40, respectively.

In one exemplary embodiment, as shown in FIGS. 2 and 3, each recoil assembly 64 may include an actuator, which are shown (in FIG. 3) as a right hydraulic cylinder 66a and a left hydraulic cylinder 66b for the pair of undercarriage assemblies 30a, 30b, respectively. The hydraulic cylinders 66a, 66b each have a fixed cylinder housing 68 having a moveable rod 70 extending therefrom. The rod 70 extends from a sealed opening 72 defined in the cylinder housing 68. In one exemplary embodiment, a first end of the rod 70 is secured to a piston (not shown) within the cylinder housing 68. A second end of each rod 70 is secured to the yoke 62 associated with the idler wheel 36. Extension of the rods 70 (i.e., movement of the rods 70 in the general direction of arrow 26) causes corresponding movement of the idler wheels 36, thereby increasing tension on the drive tracks 40. Conversely, retraction of the rods 70 (i.e., movement of the rods 70 in the general direction of arrow 28) causes corresponding movement of the idler wheels 36, thereby decreasing tension on the drive tracks 40.

In an alternative embodiment (not shown), the rod is fixed to the frame assembly of the excavator, and the cylinder housing is moveable relative to the fixed rod. In this exemplary embodiment, the cylinder housing is secured to the yoke such that extension of the cylinder housing causes corresponding movement of the idler wheel through the yoke. An advantage of this embodiment is that the seal between the rod and the cylinder housing is positioned within the cylinder housing, in a more protected environment. Generally, when the idler wheel kicks up debris from the ground, the seal is not positioned where the debris is kicked up. In an alternative of this embodiment, the recoil assembly could be a single acting cylinder having a single port, and the port could be in the rod.

The disclosed system provides a method of operating a track-type machine, such as an excavator 10, by determining an appropriate force to be applied to the idler wheel 36 based on a direction of operation of the drive wheel 34 and then applying the appropriate force to the idler wheel 36 to achieve tension on the drive track 40. Determining the appropriate force to be applied to the idler wheel 36 may include determining a first force when the drive wheel 34 is operated in a first direction and determining a second force when the drive wheel 34 is operated in a second direction, where the second direction is opposite the first direction.

In one embodiment, the first direction is in the direction from the drive wheel 34 toward the idler wheel 36 and the second direction is in the direction from the idler wheel 36 toward the drive wheel 34. In the embodiment where the

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idler wheel 36 is positioned at the front end (shown as 40a in FIGS. 1-3) of the excavator 10 and the drive wheel 34 is positioned at the rear end (shown as 40b in FIGS. 1-3) of the excavator 10, the first direction is the forward direction 26 and the second direction is the rearward direction 28.

FIG. 5 illustrates a block diagram 500 of an exemplary operation of determining a force to be applied to an idler and applying the force to the idler to achieve a tension on the drive track. The exemplary operation commences with step 510. Then, in step 520, it is determined in which direction the drive mechanism is being operated. If, in step 530, the drive mechanism is being operated in the forward direction, control then proceeds to step 550 where the position of the idler wheel is determined. If, in step 530, the drive mechanism is being operated in the reverse direction, control then proceeds to step 540, where the fluid pressure to the drive mechanism is determined. Control then proceeds to step 550 where the position of the idler is determined.

After step 550, control proceeds to step 560 where the appropriate force to apply to the idler is determined. While traveling in the forward direction, the appropriate force to be applied to the idler is based on the determined position of the idler. While traveling in the reverse direction, the appropriate force to be applied to the idler is based on the determined pressure of fluid to the drive mechanism and the determined position of the idler. If the machine is not traveling, i.e., is stopped, then the force applied to the idler is generally a single force applied to the idler so as to maintain a tension on the drive track. This single force may be higher than the force applied to the idler wheel when the machine is traveling in the forward direction and when the machine is traveling in the reverse direction. This is because when the machine is stopped, the machine is often in a work mode, when the tension on the drive track should be higher than when the machine is traveling.

Control proceeds to step 570 where the appropriate force is applied to the idler wheel. Control then continues to step 580 where the control is returned to step 510.

In one embodiment, the method of determining the force to be applied to the an idler wheel 36 and then applying the force to the idler wheel 36 to achieve tension on the drive track 40 includes utilizing one or more recoil curves, such as curves 112 and 114 shown in the graph of FIG. 4. The x-axis of the graph is the displacement (in millimeters) of the idler wheel 36. The y-axis of the graph is the force (pounds) that will be exerted on the idler wheel 36 to control recoil. The graph illustrates two curves, 112 and 114, a line 116, and a wavy line 120. The curve 112 illustrates an appropriate recoil response when the excavator 10 is traveling in the forward direction 26. The wavy line 120 illustrates an actual recoil response. The actual recoil response 120 is near the curve 112 but does not necessarily fall directly on curve 112. The curve 114 illustrates one of a plurality of recoil responses when the excavator 10 is traveling in the rearward direction 28. The line 116 illustrates the recoil response for a prior art work machine that uses a coiled spring for a tension adjustment mechanism.

While the curve 112 and the curve 114 have the same general shape, the curve 114 is translated up on the y-axis because more force needs to be applied on the idler wheel 36 to counteract the force of the drive wheel 34 pulling on the idler wheel 36 during travel in the rearward direction 28. As discussed above, during travel in the rearward direction 28, the drive wheel 34 pulls the top flight 42 of the drive track 40 around the idler wheel 36. When the idler wheel 36 is positioned at the front end of the machine, this force pulls

the idler wheel 36 toward the drive wheel 34, which aids the recoil function.

The curve 112, representing a desired recoil response curve when traveling in the forward direction 26, generally is a single curve for a single work machine. This is because, when traveling in the forward direction 26, the drive wheel 34 feeds the drive track 40 to the idler wheel 36 along the top flight 42. Thus, there is no pulling force on the idler wheel 36 by the drive wheel 34 to counteract.

In contrast, the curve 114, representing a desired recoil response curve when traveling in the rearward direction 28, may be one of a plurality of appropriate recoil response curves. The force exerted on the idler wheel 36 by the drive wheel 34 may vary depending on the drawbar load while the work machine is traveling in the rearward direction. Accordingly, there are a plurality of recoil response curves for a work machine traveling in the rearward direction that may be obtained through the present invention. Because a plurality of appropriate recoil response curves are provided for travel in the rearward direction, a work machine equipped with the present invention would operate equally well in the forward and rearward directions with high and low drawbar loads.

To graph the recoil response curves 112 and 114, data points may be plotted based on operating characteristics of the machine including the geometry of the undercarriage assembly, for example, the amount of space for a bushing to jump off the drive wheel and the wear on the track chain. The data points of the recoil response curves 112 and 114 may also be based on the drawbar load or environment conditions, such as the underfoot condition. The drawbar load is generally any force that the work machine has to overcome to move in a direction and includes, for example, the gross vehicle weight of the work machine, as well as the gross vehicle weight of any attachments attached to the work machine and any slope on which the work machine is traveling. The underfoot condition refers to the surface on which the work machine is traveling and includes pavement, soft dirt, mud, clay, and the like. Once the data points of the recoil response curves 112 and 114 are plotted on a graph, an equation may be determined that best fits those data points. This equation may be inserted as part of the algorithm that is part of the code (that is stored in a memory device 104 discussed below) that is utilized to vary the force applied to the idler wheel 36 based on the recoil response curves 112 and 114.

When the excavator 10 is traveling in the rearward direction 28, the fluid pressure to the drive motor 52a is proportional to a force pulling on the idler wheel 36 by the drive wheel 34 of the right undercarriage assembly 30a and, similarly, the fluid pressure to the drive motor 52b is proportional to a force pulling on the idler wheel 36 by the drive wheel 34 of the left undercarriage assembly 30b. For each of the undercarriage assemblies 30a, 30b, once the fluid pressure to its drive motor 52 (also referred to as "the drive pressure") is known, the fluid pressure to its hydraulic cylinder 66 may be increased to counteract the force that its drive wheel 34 exerts on its idler wheel 36 during travel in the rearward direction that tends to cause recoil. For each of the undercarriage assemblies 30a, 30b, the increase of fluid pressure to its hydraulic cylinder 66 creates another force that is applied to its idler wheel 36 in the direction 26, i.e., away from its rear drive wheel 34, to counteract the effect of the force of the drive wheel 34 pulling on the idler wheel 36.

The recoil response of the present invention is such that the external force required to cause recoil of the idler wheel

36 is the same, whether the machine is traveling forward or reverse, with high or low drawbar loads. The force applied to counteract recoil varies according to whether the machine is traveling in the forward direction 26 or the rearward direction 28.

It should also be appreciated that the amount of the drawbar load is proportional to the drive pressure because the fluid pressure to the drive motors 52a, 52b would be increased if the drawbar load increased, in order to ensure that the machine may overcome the weight of the machine and/or any attachments and be able move in a given direction. In addition, as noted above, when the machine is traveling in the rearward direction 28, the fluid pressure to the drive motors 52 is proportional to the force pulling on the idler wheel 36. Accordingly, the drive pressure is proportional to both the amount of the drawbar load and the amount of the force pulling on the idler wheel 36 to affect recoil when the machine is traveling in the rearward direction 28.

As shown in FIG. 3, in one exemplary embodiment, a controller 100 communicates with an electrically-actuated control valve assembly 80, one or more pressure sensors 84, and one or more position sensors 86 in order to maintain tension on each drive track 40 of each undercarriage assembly 30a, 30b. For example, the controller 100 may be utilized to provide an appropriate recoil response (such as curve 112 (for forward direction 26) and curve 114 (for rearward direction 28) shown in FIG. 4) for the excavator 10. Generally, the controller 100 may receive signals from the position sensors 86 representing the positions of the hydraulic cylinders 66a, 66b and signals from the pressure sensors 84 representing the fluid pressure to each of the hydraulic motors 52a, 52b of the hydraulic drive system 50. Utilizing these signals, as well as an algorithm that includes at least one recoil response curve, the controller 100 may determine whether fluid needs to be supplied to or drained from the hydraulic cylinders 66a, 66b. Upon a signal from the controller 100, the control valve assembly 80 may be utilized to either supply fluid to or drain fluid from the hydraulic cylinders 66a, 66b in order to obtain a level of tension based on the appropriate recoil response.

The control valve assembly 80 controls actuation of the hydraulic cylinders 66a, 66b in order to increase or decrease tension on its corresponding drive track 40. The control valve assembly 80 is electrically coupled to the controller 100. In one exemplary embodiment, a solenoid 82 of the control valve assembly 80 is electrically coupled to the controller 100 via a signal line 88. To increase fluid pressure in the hydraulic cylinders 66a, 66b, fluid is supplied to the hydraulic cylinders 66a, 66b from the fluid source 56 through the control valve assembly 80. To decrease fluid pressure in the hydraulic cylinders 66a, 66b, fluid is drained from the hydraulic cylinders 66a, 66b to the fluid reservoir 58 through the control valve assembly 80.

In one exemplary embodiment, the control valve assembly 80 includes an independent metering valve (IMV) assembly. The IMV assembly may be operated to fluidly couple the hydraulic cylinders 66a, 66b so as to increase or decrease fluid pressure in the hydraulic cylinders 66a, 66b to increase or decrease, respectively, tension on the drive track 40. The IMV assembly may be an electrically-actuated valve assembly that includes a pressure sensor 84 therein.

The one or more pressure sensors 84 are utilized to sense pressure in one or more fluid lines. In an exemplary embodiment, one pressure sensor 84 senses the fluid pressure to the hydraulic motor 52a (that drives the drive wheel 34 for the undercarriage assembly 30a), while a second

pressure sensor 84 senses the fluid pressure to the hydraulic motor 52b (that drives the drive wheel 34 for the undercarriage assembly 30b). Each pressure sensor 84 may be electrically coupled to the controller 100 via a signal line 90. Thus, in the embodiment including two pressure sensors 84, output signals generated by the pressure sensors 84 are communicated to the controller 100 via a pair of signal lines 90.

The one or more position sensors 86 may be located such that they can monitor the position of a number of undercarriage components relative to one another. At least one of the position sensors 86 is provided to sense the position of one rod 70 relative to its corresponding housing 68 of one of the hydraulic cylinders 66a, 66b. In one exemplary embodiment, two position sensors 86 are provided, each to sense the position of each rod 70 relative to its corresponding housing 68 of each of the hydraulic cylinders 66a, 66b. The position sensors 86 may be provided as any type of sensor which is capable of sensing the position of the rods 70. It should be appreciated that the position of the idler wheels 36 may be ascertained from the position of the rod 70 relative to its corresponding housing 68. In another exemplary embodiment, at least one of the position sensors 86 may be provided to sense the position of at least one of the idler wheels 36. For example, the position sensors may be magnetostrictive position sensors that are part of the hydraulic cylinders 66a, 66b or linear displacement transducers.

Each position sensor 86 may be electrically coupled to the controller 100 via a signal line 92 or, in the alternative, via wireless communication (not shown). Thus, in the embodiment including two position sensors 86 for sensing each of idler wheels 36 of both undercarriage assemblies 30a, 30b, output signals generated by the position sensors 86 are communicated to the controller 100 via a pair of signal lines 92. Such output signals may be generated and thereafter communicated by the position sensors 86 in numerous forms. For example, the position sensors 86 may generate output signals in the form of an analog DC voltage, or in the form of a signal utilizing current-to-pulse signal timing or pulse width modulation.

The controller 100 includes electrical components commonly found in other work machine controllers, such as a microprocessor 102, a memory device 104, and an interface circuit 106. The controller 100 may be a dedicated controller for controlling the components shown in FIG. 3. In the alternative, the controller 100 may be integrated into another controller associated with the excavator 10, such as an engine controller (not shown), transmission controller (not shown), or an implement controller (not shown).

The interface circuit 106 converts the output signals from the one or more pressure sensors 84 and the one or more position sensors 86 into signals that are suitable for presentation to an input of the microprocessor 102. It should be appreciated that the magnitude of the voltage generated by each pressure sensor 84 is indicative of the hydraulic fluid pressure to one of the hydraulic motors 52a, 52b, while the magnitude of the voltage generated by each position sensor 86 is indicative of the position of one of the rods 70 within its corresponding cylinder housing 68 or, more generally, the position of one of the idler wheels 36.

The interface circuit 106 also converts output signals generated by the microprocessor 102 into signals which are suitable for use by the solenoid 82 associated with the control valve assembly 80. In particular, the interface circuit 106 may convert the output signals from the microprocessor

102 into an analog actuation pulse which actuates the solenoid 82, thereby positioning the control valve assembly 80 into one of its actuated positions in order to cause extension or retraction of the hydraulic cylinders 66a, 66b, as described above. It should be appreciated that the interface circuit 106 may be embodied as a discrete device or a number of devices, or may be integrated into the microprocessor 102.

The memory device 104 is provided to store the code or set of instructions that are executed by the controller 100 during operation of the track tensioning assembly 60. For example, the memory device 104 is utilized to store the code containing an algorithm that includes a plurality of appropriate recoil curves, such as a recoil curve 112 (see FIG. 4) for travel in the forward direction 26 and a plurality of recoil curves 114 (see FIG. 4) for travel in the rearward direction 28, for a variety of parameters. Moreover, operation parameters may also be stored in the memory device 104. The memory device may be embodied as any known memory device, such as RAM and/or ROM devices.

As discussed above, in an exemplary embodiment, the controller 100, along with the control valve assembly 80, the pressure sensor(s) 84, and the position sensor(s) 86, are utilized to ensure that the recoil response of a work machine is at or near a level of tension based on the desired recoil curves 112 and 114 for that machine. Again, the actual recoil response may not fall directly on curve 112 or 114, but may fall generally around these curves, such as shown in the wavy line 120 that follows the general shape of curve 112.

As noted above, there are a plurality of recoil response curves 114 for a single work machine. In one embodiment, the controller 100 first determines which of the available recoil response curves is the appropriate recoil response curve. For example, the controller 100 may select the appropriate recoil response curve 114 based on the reverse drive pressure (the drive pressure to the hydraulic motors 52a, 52b when the excavator is traveling in the rearward direction 28) sensed by the pressure sensor 84, because the reverse drive pressure is proportional to the force pulling on the idler wheel 36. Thus, the appropriate recoil response curve 114 selected is based on compensating or counteracting for that force pulling on the idler wheel 36. As discussed above, the appropriate recoil response curve 114 selected is indirectly reflective of the drawbar load and the underfoot condition because each of the available recoil response curves include data points that are reflective of the drawbar load and the underfoot condition.

In an exemplary embodiment, when the reverse drive pressure to the drive motors 52a, 52b is continuously sensed by pressure sensors 84, the controller 100 continuously selects an appropriate recoil response curve 114 for each of the undercarriage assemblies 30a, 30b, respectively. A later selected appropriate recoil response curves 114 may be similar to an earlier curve if conditions are relatively constant or may be quite different if conditions change, such as, for example, traveling on a different surface (a different underfoot condition).

Optionally, applying the appropriate force to the idler wheel 36 based upon a recoil curve 112 or 114 includes sensing a position of the idler wheel 36 to determine the amount of recoil of the idler wheel 36, plotting the sensed position of the idler wheel 36 on the recoil curve 112 or 114, and varying the force to the idler wheel 36 based on the recoil curve 112 or recoil curve 114.

More particularly, the position sensor 86 senses the position of rod 70 within its corresponding housing 68 of at least



one of the hydraulic cylinders 66a, 66b. In an exemplary embodiment, two position sensors 86 each sense the position of a rod 70 within its corresponding housing 68 of both hydraulic cylinders 66a, 66b. It should be appreciated that the position of the idler wheel 36 is dependent on the position of the rod 70. Thus, once the position of the rod 70 relative to its corresponding housing 68 is determined, then the position of the idler wheel 36 may be determined or, in other words, the amount of recoil of the idler wheel 36. In the exemplary embodiment, because both hydraulic cylinders 66a, 66b are being sensed, the amount of recoil of both idler wheels 36 may be determined.

Once the amount of recoil of the idler wheel 36 is inputted into the controller 100, the controller 100 compares the position of the idler wheel 36 to the recoil curve 112 (when the excavator 10 is traveling in the forward direction 26) or the appropriate recoil curve 114 that the controller 100 has selected for that situation (when the excavator 10 is traveling in the rearward direction 28). In the exemplary embodiment, because the amount of recoil of both idler wheels 36 are determined, the positions of both of the idler wheels 36 are compared to the recoil curve 112 or 114 for that undercarriage assembly 30a, 30b.

For each undercarriage assembly 30a, 30b, the amount of idler wheel 36 recoil is a position value (on the x-axis) on a graph, such as shown in FIG. 4. Knowing that idler wheel 36 position, it is determined how much to vary the force applied to the idler wheel 36 by determining what the appropriate force on the idler wheel 36 should be based on the recoil curve 112 (when traveling in the forward direction 26) or the appropriate recoil curve 114 (when traveling in the rearward direction 28). For example, if the idler wheel 36 recoil is around 20 mm, then the amount of force that should be applied to the idler wheel 36 is shown as  $X_f$  in FIG. 4 during travel in the forward direction 26 and is shown as  $X_r$  during travel in the rearward direction 28. In the exemplary embodiment, the amount of force to be applied to the idler wheel 36 is determined for both idler wheels 36 of both undercarriage assemblies 30a, 30b based on the recoil curve 112 or the appropriate recoil curve 114 that the controller has selected for each of the undercarriage assemblies 30a, 30b.

After it is determined how much force should be applied to the idler wheel 36 based on the recoil response curve 112 or the appropriate recoil response curve 114, the controller 100 signals the control valve assembly 80 to either supply fluid to or drain fluid from one or both recoil assemblies 64 in order to move one or both rods 70 relative to its or their corresponding housings 68 in order to exert more force or less force, respectively, on the idler wheels 36 of one or both of the undercarriage assemblies 30a, 30b. During travel in the rearward direction 28, this additional force on the idler wheel 36 is a force that counteracts the effect of the force exerted on the idler wheel 36 by the drive wheel 34 during travel in the rearward direction 28. Accordingly, in the manner described above, the controller 100 controls operation of the control valve assembly 80 so as to increase fluid pressure in the hydraulic cylinder 66a and/or hydraulic cylinder 66b to exert more force on one or both of the idler wheels 36. This force is exerted on the idler wheels 36 in the forward direction 26 to counteract the force that the rear drive wheel 34 exerts on the idler wheels 36 during travel in the rearward direction 28.

#### INDUSTRIAL APPLICABILITY

The present invention allows for determining the appropriate force to be applied to the idler wheel 36 based on the

direction of operation of a track-type work machine and applying the appropriate force to the idler wheel 36 to achieve a predetermined tension on the drive track 40. When the track-type work machine is traveling in the direction from the drive wheel 34 to the idler wheel 36, the appropriate force to the idler wheel 36 may be applied in a variable manner based on a recoil curve, such as curve 112. When the track-type work machine is traveling in the direction from the idler wheel 36 to the drive wheel 34, the appropriate force to the idler wheel 36 may be applied in a variable manner by, first, determining the pressure to the drive wheel to select an appropriate recoil curve, such as curve 114, then determining the idler position, and then using the determined idler position value to determine the appropriate force based on the selected recoil curve.

With respect to the excavator 10 of the exemplary embodiment, the controller 100 communicates with the control valve assembly 80, the pressure sensors 84, and the position sensors 86 in order to ensure that the recoil response of the excavator 10 complies with the appropriate recoil curves for that excavator 10 in a particular situation. The pressure sensors 84 sense the fluid pressure to both hydraulic motors 52a, 52b of the hydraulic system 50, and the values of the sensed fluid pressures are inputted to the controller 100. Similarly, the position sensors 86 sense the position of the rod 70 relative to its corresponding housing 68 for both of the undercarriage assemblies 30, and these position values are also inputted to the controller 100. The controller 100 utilizes these values in an algorithm contained within the memory device 104 of the controller 100. The algorithm within the memory device 104 includes therein various operating parameters, including a plurality of recoil response curves for when the excavator 10 is traveling in the rearward direction 28 that are dependent, at least in part, on the drawbar load and environmental conditions. Again, there is generally only one desired recoil response curve for an excavator 10 that is traveling in the forward direction 26.

Accordingly, during travel in the forward direction 26, the algorithm includes a recoil response curve 112. During travel in the rearward direction 28, from the plurality of recoil response curves available in the algorithm, the controller 100 provides an appropriate recoil response curve 114 (with respect to each idler wheel 36 for each of the undercarriage assemblies 30a, 30b) based on the drive pressure that the pressure sensor 84 senses is going to both hydraulic drive motors 52a, 52b. This drive pressure is proportional to the force pulling on the idler wheel 36 when the excavator is traveling in the rearward direction 28. Thus, the controller 100 provides the appropriate recoil response curve 114 for each idler wheel 36 to compensate for that force pulling on the idler wheel 36 for each of the undercarriage assemblies 30a, 30b.

For both undercarriage assemblies 30a, 30b, the controller determines how much the idler wheel 36 is recoiled using the position sensors 86 that sense the position of the rods 70 relative to their corresponding housings 68 of both hydraulic cylinders 66a, 66b. Knowing how much the idler wheel 36 is recoiled of each undercarriage assembly 30a, 30b, the controller 100 compares that sensed position value of the idler wheel 36 with the recoil response curve 112 (when traveling in the forward direction 26) or 114 (when traveling in the rearward direction 28) for each undercarriage assembly 30a, 30b. As stated above, as an example, using the recoil response curves 112 and 114 shown in the graph of FIG. 4, if the idler wheel 36 recoil is around 20 mm, then the amount of force that is appropriate to be exerted on the idler wheel 36 is shown as  $X_f$  in FIG. 4 when traveling in the

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forward direction 26 and is shown as  $X_r$  in FIG. 4 when traveling in the rearward direction 28.

To achieve that appropriate force on the idler wheel 36, the controller 100 outputs signals to the control valve assembly 80. Upon receiving the output signal from the controller 100, the control valve assembly 80 supplies fluid to or drains fluid from one or both hydraulic cylinders 66a, 66b to achieve that appropriate force.

In contrast to the currently available work machines, the present invention allows for a recoil response for both forward and rearward directions. By monitoring the system conditions, such as drive pressure, the present invention takes into account factors such as drawbar load and underfoot conditions in selecting the appropriate recoil response curve. This allows for appropriate tensioning of the track chain during work operation and travel, thereby resulting in extending the useful life of the machine. While the disclosed embodiment refers to an excavator, it should be understood that the present invention has wider application to various types of tracked vehicles.

Other aspects and features of the present invention can be obtained from a study of the drawings, the disclosure, and the appended claims.

What is claimed is:

1. A method of operating a track-type machine having a drive wheel and an idler, the method comprising:

operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine;

determining a direction of operation of the drive wheel; sensing a pressure of fluid being used to operate the drive wheel;

determining a force to be applied to the idler based on the determined direction of operation of the drive wheel and, depending on the determined direction of operation, the sensed pressure of fluid being used to operate the drive wheel;

applying the force to the idler.

2. The method of claim 1, wherein said determining a force includes selecting a recoil curve from a plurality of recoil curves based on the sensed pressure of fluid being used to operate the drive wheel and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve.

3. The method of claim 2, wherein the direction of operation is in a direction from the idler toward the drive wheel.

4. The method of claim 1, wherein said applying the force includes operating a valve assembly to control fluid pressure within an actuator associated with the idler.

5. The method of claim 1, wherein said determining a force includes determining a first force when the drive wheel is operated in a direction from the drive wheel toward the idler and determining a second force differing from the first force when the drive wheel is operated in a direction from the idler toward the drive wheel.

6. The method of claim 1, wherein the force applied to the idler is a function of a drawbar load of the machine.

7. A work machine, comprising:

a source of pressurized fluid;

a fluid reservoir;

a drive track;

an idler;

a drive wheel, the drive wheel being operable to advance the drive track around the drive wheel and the idler;

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an actuator mechanically coupled to the idler, the actuator being operable to increase and decrease a force being applied to the idler;

a valve assembly operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir;

a pressure sensor configured to sense the pressure of fluid being directed from the source of pressurized fluid to the drive wheel; and

a controller configured to operate the valve assembly to apply a force to the idler based on a direction of operation of the drive wheel and, depending on the determined direction of operation, the sensed pressure of fluid being directed to the drive wheel.

8. A The work machine of claim 7, further including a position sensor configured to sense a position of the idler, and

wherein the controller is configured to operate the valve assembly to apply the force to the idler by selecting a recoil curve from a plurality of recoil curves based on the sensed pressure of fluid being directed to the drive wheel and by selecting the force to be applied to the idler based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve.

9. The work machine of claim 1, wherein the drive wheel is operable to advance the drive track in a first direction that is associated with movement of the work machine in a direction from the drive wheel toward the idler and in a second opposing direction that is associated with movement of the work machine in a direction from the idler toward the drive wheel, and

wherein the controller is configured to operate the valve assembly to apply a first force when the drive wheel is operated in the first direction and a second force when the drive wheel is operated in the second direction, the first force differing from the second force.

10. The work machine of claim 7, wherein the force applied to the idler is a function of a drawbar load of the machine.

11. A method of operating a track-type machine having a drive wheel at a first end of the track-type machine and an idler at a second end of the track-type machine, the method comprising:

operating a drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine, the drive wheel being operable in a first direction associated with movement of the track-type machine in a direction from the drive wheel toward the idler and in a second direction associated with movement of the track-type machine in a direction from the idler toward the drive wheel;

determining a force to be applied to the idler based on a direction of operation of the drive wheel and a sensed position of the idler when the drive wheel is operated in the first direction, and, when the drive wheel is operated in the second direction, based on a direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and a sensed position of the idler; and

applying the force to the idler.

12. A method of operating a track-type machine having a drive wheel and an idler, the method comprising:

operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine;

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determining a direction of operation of the drive wheel;  
determining an amount of recoil of the idler;

determining, when the drive wheel is operated in a first direction, a force to be applied to the idler based on the determined direction of operation of the drive wheel and the amount of recoil of the idler; and applying the force to the idler. 5

13. The method of claim 12, further including, when the drive wheel is operated in a second direction opposite the first direction, sensing a pressure of fluid being used to operate the drive wheel, 10

wherein said force to be applied is determined based on the determined direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and the amount of recoil of the idler. 15

14. The method of claim 12, wherein said determining the amount of recoil includes sensing a position of the idler.

15. The method of claim 12, wherein the force applied to the idler is a function of a drawbar load of the machine. 20

16. The method of claim 12, wherein said applying the force includes operating a valve assembly to control fluid pressure within an actuator associated with the idler.

17. A work machine, comprising:

a source of pressurized fluid; 25

a fluid reservoir;

a drive track;

an idler;

a drive wheel, the drive wheel being operable to advance the drive track around the drive wheel and the idler;

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an actuator mechanically coupled to the idler, the actuator being operable to increase and decrease a force being applied to the idler;

a valve assembly operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir; and

a controller configured to determine a direction of operation of the drive wheel and an amount of recoil of the idler, and to operate the valve assembly, when the drive wheel is operated in a first direction, to apply a force to the idler based on the determined direction of operation of the drive wheel and the amount of recoil of the idler.

18. The work machine of claim 17 further including a pressure sensor configured to sense the pressure of fluid being directed from the source of pressurized fluid to the drive wheel, 15

wherein, when the drive wheel is operated in a second direction opposite the first direction, said force to be applied is determined based on the determined direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and the amount of recoil of the idler.

19. The work machine of claim 17, further including a position sensor configured to sense a position of the idler, wherein the controller determines the amount of recoil of the idler based on a sensed position of the idler.

20. The work machine of claim 17, wherein the force applied to the idler is a function of a drawbar load of the machine.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 6,948,783 B2  
DATED : September 27, 2005  
INVENTOR(S) : Brian D. Hoff

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13,

Line 37, after "operate the drive wheel;" , insert -- and --.

Column 14,

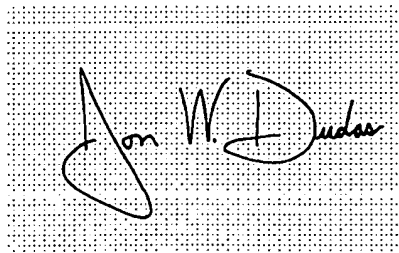
Line 26, delete "claim 1," and insert -- claim 7, --.

Column 15,

Line 6, after "and" (second occurrence), the phrase "applying the force to the idler." should begin a new paragraph.

Signed and Sealed this

Seventeenth Day of January, 2006

A handwritten signature in black ink, reading "Jon W. Dudas", is written over a rectangular area filled with a fine grid of dots. The signature is stylized, with the first name "Jon" and last name "Dudas" clearly legible, and "W." in the middle.

JON W. DUDAS

*Director of the United States Patent and Trademark Office*

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